RD
651
U58
fasc.3
suppl.
1982

TUMORS
of the
PERIPHERAL NERVOUS SYSTEM

by

JAMES C. HARKIN, M.D.

and

RICHARD J. REED, M.D.

Supplement

AFIP

ATLAS OF TUMOR PATHOLOGY

Second Series

Supplement

TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

Fascicle 3, Second Series

by

RICHARD J. REED, M.D.
Department of Pathology
Tulane University School of Medicine
New Orleans, Louisiana 70112

and

JAMES C. HARKIN, M.D.
Department of Pathology
Tulane University School of Medicine
New Orleans, Louisiana 70112

Published by the
ARMED FORCES INSTITUTE OF PATHOLOGY
Washington, D.C.

Under the Auspices of
UNIVERSITIES ASSOCIATED FOR RESEARCH AND EDUCATION IN PATHOLOGY, INC.
Bethesda, Maryland
1983

Accepted for Publication
1982

For sale by the Armed Forces Institute of Pathology
Washington, D.C. 20306
ISSN 0160–6344

ATLAS OF TUMOR PATHOLOGY

Sponsored by

AMERICAN CANCER SOCIETY
ARMED FORCES INSTITUTE OF PATHOLOGY
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH
UNIVERSITIES ASSOCIATED FOR RESEARCH AND EDUCATION IN PATHOLOGY, INC.

EDITOR
WILLIAM H. HARTMANN, M.D.
Professor and Chairman, Department of Pathology
Vanderbilt University School of Medicine
Nashville, Tennessee 37232
Area Code 615 — 329-2541

COEDITOR
WILLIAM R. COWAN, COLONEL, USAF, MC
Armed Forces Institute of Pathology
Washington, D.C. 20306

EDITORIAL ADVISORY COMMITTEE

Harlan I. Firminger, M.D.	University of Colorado Medical Center Denver, Colorado 80220
David G. Freiman, M.D.	Harvard Medical School and Beth Israel Hospital Boston, Massachusetts 02215
Robert V. P. Hutter, M.D.	St. Barnabas Medical Center Livingston, New Jersey 07039
F. K. Mostofi, M.D.	Armed Forces Institute of Pathology Washington, D.C. 20306
Alan Rabson, M.D.	National Cancer Institute, National Institutes of Health Bethesda, Maryland 20205
Richard J. Reed, M.D.	Tulane University School of Medicine New Orleans, Louisiana 70112
Juan Rosai, M.D.	University of Minnesota Medical School Minneapolis, Minnesota 55455

EDITOR'S NOTE

This is the third Supplement to the Fascicles of the Second Series of the Atlas of Tumor Pathology. Although planning for a Third Series is under way, availability is as yet at some time in the future. Because some of the Fascicles of the current Series are ten or more years old and because of advances in diagnostic anatomic pathology, this Series of Supplements seems appropriate. We hope you find them useful.

Each Supplement will be written by the authors of the Fascicles of the Second Series and subject to the usual review practices of the Editorial Advisory Committee and the Editor. It is unlikely there will be a Supplement for each Fascicle. As always, your comments are invited.

William H. Hartmann, M.D.

To my beloved son Jay

R.J.R.

Supplement

TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

Fascicle 3, Second Series

Contents

	Page No.
Anatomic Features	S-1
Interdigital Neuritis	S-3
Tumorous Dysplasia and Hyperplasia of Axons	S-6
Neuromas	S-6
Benign Tumors of Nerve Sheath Origin	S-11
Schwannoma	S-11
Perineurial Neoplasms	S-14
Storiform Perineural Fibroma	S-15
Perineurial Myxoma	S-16
Neuromesenchyme	S-19
Tumorous Dysplasias of the Neurosustentacular System	S-22
Circumscribed Neurofibroma	S-22
Paraneurofibroma	S-24
Plexiform Epithelioid Neurofibroma	S-25
Symmetrical Neurofibroma	S-25
Primary Malignant Tumors of Nerves and Nerve Sheaths	S-28
Malignant Neuromesenchymoma	S-29
Malignant Epithelioid Schwannoma	S-30
Diffuse Epithelial Malignant Schwannoma	S-35
Neuroepithelioma of Peripheral Nerves	S-39
Malignant Undifferentiated Small Cell Tumor of Peripheral Nerves	S-39
Neurotropic Melanoma	S-41
The Spindle Melanocyte, Desmoplasia, and Neurotropism	S-41
Precursors of Neurotropic Melanomas	S-42
Clear Cell Sarcoma	S-47
Miscellaneous	S-48
Index	S-51

Supplement

TUMORS OF THE PERIPHERAL NERVOUS SYSTEM

ANATOMIC FEATURES

Anatomy. A peripheral nerve is composed of axons, sheath (Schwann) cells, a fiber-poor mucinous matrix (endoneurium), and an enveloping tube (perineurium). A column of sheath cells and their axons form a primary unit. The structures confined by a perineurium constitute a nerve bundle (fig. 3*). Neighboring bundles are encased in a dense fibrous matrix, the epineurium (fig. 4).

Axons vary in size and function. They are grouped in two categories, reflecting in part their diameters and in part the relationship between axons and sheath cells. For axons with small diameters, a single sheath cell encloses multiple axons. For axons with large diameters, the relationship between an axon and a sheath cell is 1:1, and the latter provides a myelin sheath for the former (fig. 1).

The **sheath cells** are bipolar and are arranged end to end in columns (fig. 2). They have complex interdigitating cell processes. Each column, as a file of single cells, has a supporting sheath of reticular fibers and, ultrastructurally, has a continuous basal lamina (fig. 5). The combination of collagen fibrils (reticular fibers) and basal lamina are combined at the level of the light microscope as a basement membrane. Sheath cells are facultative fibroblasts and histiocytes. The histiocytic role is demonstrated in a process such as wallerian degeneration (figs. 11, 12). Histiocytic Schwann cells retain their basal lamina.

The **endoneurium** is a specialized, mucinous matrix that is relatively free of collagen fibers. Ultrastructurally, most of its collagen fibrils represent constituents of the fibrous membranes of sheath cells and measure 300-400 Å in diameter (Friede and Bischhausen; Junqueira et al.). Fibrous, long-spacing collagen and tubular microfibrils which resemble the fibrillar component of elastic fibers are additional components (Thomas; Lassmann et al.). The endoneurial matrix is fibromucinous. It serves as a lubricant between the aggregates of primary units (axons and their ensheathing Schwann cells) and the perineurial tube. Fibroblasts, occasional histiocytes, and mast cells reside in the matrix.

The **perineurium** is a fibrous tube whose peripheral terminal is open. Proximally, it blends with the leptomeninges. The perineurial cell is thin and flat. It is a close relative of the sheath cell. It has rigid cytoplasmic extensions and ultrastructurally forms tight junctions with neighboring cells. The cytoplasm of the perineurial cell has a discontinuous basal lamina and contains numerous micropinocytotic vesicles

*Figures 1 through 197 appear in Fascicle 3, Second Series, Tumors of the Peripheral Nervous System.

(Burkel; Shantha and Bourne). Near the endoneurium, perineurial cells form a continuous layer with relatively scant intercellular fibrous matrix. In this location, the arrangement of perineurial cells has been compared to an epithelial layer (Shantha and Bourne). The perineurium functions as a diffusion barrier.

The neurosustentacular system is composed of the cells and the matrices which support axons (Table 1).

Table 1

THE NEUROSUSTENTACULAR SYSTEM

1. Sheath (Schwann) cell fascicles and their fibrous membranes
2. Endoneurial matrix and supporting cells
   a. fibroblasts
   b. mast cells
3. Perineurium
   a. a tubular condensation of fibrous tissue
   b. supporting perineurial cells

The **epineurium** is a condensation of dense fibrous tissue. It has no distinguishing characteristics other than the support it offers neighboring nerve bundles. The epineurial fibrous matrix and its supporting fibroblasts are excluded from the specialized components of the neurosustentacular system.

References

Burkel, W. E. The histological fine structure of perineurium. Anat. Rec. 158:177-190, 1967.

Friede, R. L. and Bischhausen, R. The organization of endoneural collagen in peripheral nerves as revealed with the scanning electron microscope. J. Neurol. Sci. 38:83-88, 1978.

Junqueira, L. C. U., Montes, G. S., and Kristán, R. M. The collagen of the vertebrate peripheral nervous system. Cell Tissue Res. 202:453-460, 1979.

Lassmann, G., Lassmann, H., and Stockinger, L. Morton's metatarsalgia: Light and electron microscopic observations and their relation to entrapment neuropathies. Virchows Arch. [Pathol. Anat.] 370:307-321, 1976.

Shantha, T. R. and Bourne, G. H. The Perineural Epithelium — A New Concept, pp. 379-459. In: Structure and Function of the Nervous Tissue. Vol. 1. Bourne, G. H. (Ed.). New York-London: Academic Press, 1968.

Thomas, P. K. The connective tissue of peripheral nerves: an electron microscope study. J. Anat. 97:34-44, 1963.

INTERDIGITAL NEURITIS
(MORTON'S NEUROMA)

Definition. Interdigital neuritis is a painful interdigital disease that is manifested histologically by demyelination of the interdigital nerve, an occlusive endarteritis of the neighboring artery, a fibrinous synovitis and epineuritis, and epineurial elastolysis.

The interdigital nerve and neighboring structures are subjected to compression and shearing forces between the metatarsal heads (impingement). It is difficult to ignore these forces in the pathogenesis of the interdigital neuritis (impingement neuropathy) (Dellon and Seif; Neary and Eames; Neary et al.). Other contributing processes include ischemia and inflammation. Compromised arterial vessels and fibrinoid necrosis are common features.

Histology. The components of the lesion are listed in Table 2.

Table 2

COMPONENTS OF INTERDIGITAL NEURITIS

1. Neuritis
   a. demyelination (fig. 15)
   b. focal dissolution of Schwann cell fascicles (naked axons)
   c. fibromucinous discs (intravaginal hyaline system of Renaut [Lassman et al.; Renaut; Reed and Bliss]; figs. 15–17)
   d. proliferation and hyalinization of endoneurial vessels (fig. 17)
   e. perineurial fibrosis (fig. 15)
   f. endoneurial fibrosis (fig. 15)
   g. conversion of axons to a population with small diameters
   h. reduction in number of axons
2. Obliterative arteritis
   a. proliferative endarteritis
   b. eccentric lysis of elastic lamina
   c. fibrous obliteration of lumen and focal eccentric mural fibrosis
   d. coiled remnants of internal elastic lamina in the fibrous defects
3. Epineurial elastolysis
4. Proliferative fibrinous bursitis
5. focal epineurial clefts with palisaded histiocytes and deposits of fibrinoid
6. Hyperelastosis and variable elastolysis in adjacent soft tissue (Reed and Bliss)
   a. "pale" elastica
   b. bilaminar elastica: core of elastin and shell of "fibrinoid" (fig. 198)

Bordering the zone of complete elastolysis, the elastica shows distinctive alterations. Focally, some of the fibers are fibrillated or show uniform pallor with Masson's trichrome stain. Some have a distinctive bilaminar quality (fig. 198). The inner core has the tinctorial qualities of elastin. The outer shell is irregularly globular and has the tinctorial qualities of fibrinoid (Reed and Bliss). The bilaminar fibers are similar to those seen in elastofibroma dorsi and cutaneous nevus elasticus.

In the interdigital nerve, peculiar disc shaped areas of mucinous or hyaline degeneration are a common feature (Lassmann et al.; figs. 15, 16). They are hypocellular and contain scattered stellate cells with elongated delicate processes. The long axis of the disc parallels the long axis of the involved nerve (fig. 15). At the extremity of the disc, it is sometimes possible to demonstrate continuity with the myelin sheath of a primary unit. The fibrous membrane of the interrupted sheath is splayed over the surface of the disc. In the mucinous stage, some of the discs contain scattered naked axons. Vacuolated cells (cellules godronné of Renaut) are occasionally a feature of the mucinous lesions. With an elastic stain (Verhoeff-van Gieson stain), the discs have a faint fibrillar positivity. They mature into dense hyalinized fibrous tissue containing

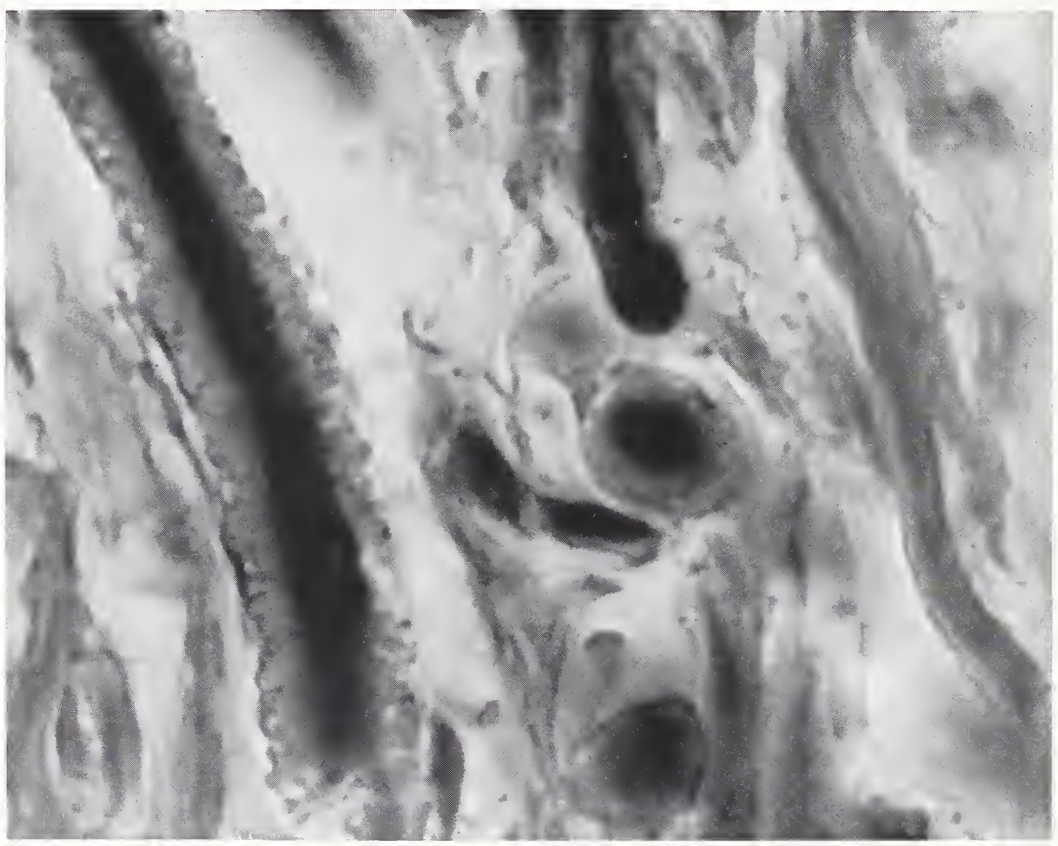

Figure 198
INTERDIGITAL NEURITIS
In the fibrous tissue bordering some Morton's neuromas, elastic fibers have a bilaminar quality. With the Verhoeff-van Gieson stain, the outer shell has fibrinoid qualities (yellow) and the inner core is black. X1840.

stellate cells with argyrophilic processes (fig. 199). Ultrastructurally, the discs contain numerous tubular microfibrils (Lassmann et al.). The discs are common in interdigital neuritis, but are not diagnostic. They share features with the lesions described by Renaut and are occasionally an incidental finding in otherwise normal nerves.

Ultrastructurally, entrapment neuropathy shows focal herniation of Schwann cells from axons at nodes of Ranvier. The Schwann (myelin) sheath at first is attenuated and eventually disappears (Neary et al.).

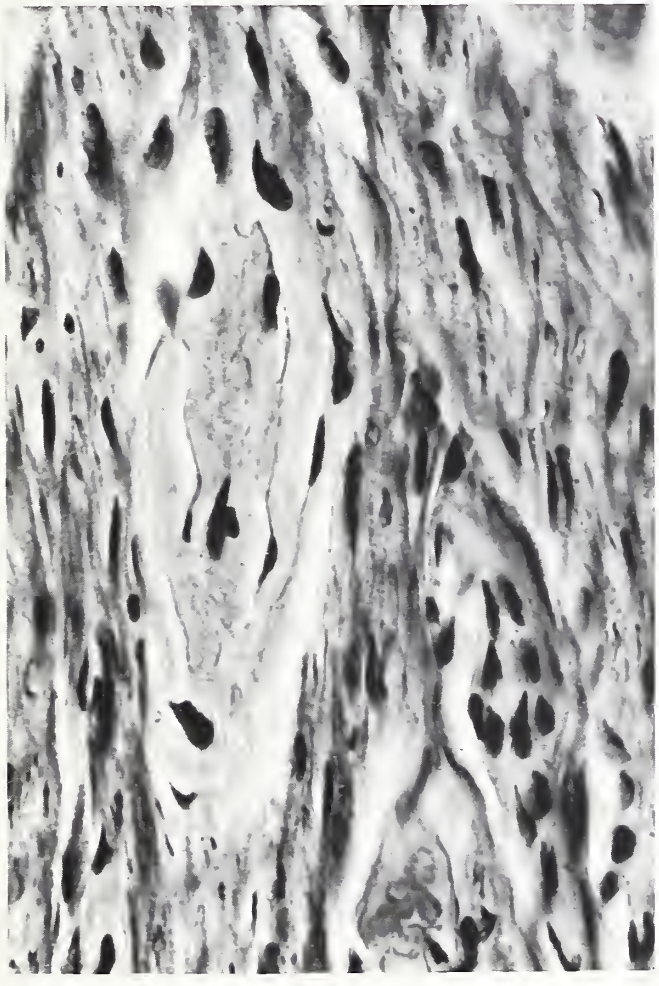

Figure 199
INTERDIGITAL NEURITIS
In the hyaline nodule near the center of the field, cells have elongated delicate argyrophilic processes. Bodian method. X600.

Summary. The syndrome of interdigital neuritis is an expression of direct mechanical pressure on a bursa, on interdigital vessels, and on a nerve. The impingement of soft tissues between apposing bony surfaces activates inflammatory mediators with the release of lytic enzymes and with altered vascular permeability. Inflammation is manifested by a fibrinous bursitis, fibrinous clefts in mesenchyme, and elastolysis. In the latter process, surviving elastic fibers show tinctorial and morphologic alterations. The arteries are compromised by proliferative changes and by proximity to foci of inflammation. The lack of proliferative changes in the altered nerve may in part express an impaired arterial supply. Finally, the histiocytic function of Schwann cells may contribute to the lytic process in the connective tissue by the release and diffusion of lytic enzymes into the soft tissue.

References

Asbury, A. K. Renaut bodies. A forgotten endoneurial structure. J. Neuropathol. Exp. Neurol. 32:334-343, 1973.

Dellon, A. L. and Seif, S. S. Anatomic dissections relating the posterior interosseous nerve to the carpus, and the etiology of dorsal wrist ganglion pain. J. Hand Surg. 3:326-332, 1978.

Lassmann, G., Lassmann, H., and Stockinger, L. Morton's metatarsalgia: Light and electron microscopic observations and their relation to entrapment neuropathies. Virchows Arch. [Pathol. Anat.] 370:307-321, 1976.

Neary, D. and Eames, R. A. The pathology of ulnar nerve compression in man. Neuropathol. Appl. Neurobiol. 1:69-88, 1975.

_____, Ochoa, J., and Gilliatt, R. W. Sub-clinical entrapment neuropathy in man. J. Neurol. Sci. 24:283-298, 1975.

Reed, R. J. and Bliss, B. O. Morton's neuroma: Regressive and productive intermetatarsal elastofibrositis. Arch. Pathol. 95:123-129, 1973.

Renaut, R. Researches sur quelques points particuliers d'histologie de nerfs. Arch. Physiol. 8:180-190, 1887.

TUMOROUS DYSPLASIA AND HYPERPLASIA OF AXONS

NEUROMAS

Definition. A neuroma is a tumorous hyperplasia of axons with compensatory hyperplasia of supporting sheath cells (Reed et al.).

In neuromas, axons are focally hyperplastic. Schwann cells invariably are also hyperplastic, but their presence is interpreted as a secondary response to the abnormal component of axons. Neuromas are either spontaneous dysplasias or self-limited acquired hyperplasias. If the proliferation of axons occurs in the endoneurial space within the confines of the perineurium, the resulting lesion is an encapsulated spontaneous neuroma. If the proliferating axons extend through a defect in the perineurium into the adjacent mesenchyme, it is an infiltrating acquired (traumatic or amputation) neuroma.

The axons in an infiltrating neuroma invade mesenchyme and repeatedly branch (fig. 13). The infiltrating neuroma stabilizes once the reacting neurosustentacular cells have reestablished perineurial sheaths and have ensheathed the naked axons.

In an encapsulated neuroma, axons focally proliferate within the confines of an intact neurosustentacular system.

Genetic Correlations. In several genetic diseases, tumorous dysplasias are relatively confined to a local anatomic site. In the skin, the butterfly area of the face is a favored site. The angiofibromas of the tuberous sclerosis complex and hamartomas of the appendages, including tricholemmomas of Cowden's syndrome, are examples of genetic tumorous dysplasias that are confined to or prominent within the butterfly area of the face (Reed). The cutaneous lesions in each of these genetic disorders are matched by sporadic, histologically identical lesions that are confined to the butterfly area of the face but are not associated with the stigmata of a genetic disease. A solitary melanocytic angiofibroma (fibrous papule) is the histologic image of the angiofibromas (adenoma sebaceum) of the tuberous sclerosis complex. A solitary tricholemmoma is a histologic image of some of the lesions in Cowden's syndrome. These two histologic images of genodermatoses have the same limited distribution (butterfly area of the face) as their genetic counterparts. The solitary encapsulated neuroma has a predilection for the butterfly area of the face and is a histologic image of mucocutaneous lesions of the mucosal neuroma syndrome (Reed et al.; figs. 100, 101).

Histology. A solitary encapsulated neuroma is a bulbous expansion of a terminal cutaneous nerve (Dupré et al.; fig. 200). It is sometimes possible to microscopically trace the progressive transformation of a small nerve proximal to the neuroma (fig. 201). The altered nerve usually courses over the superficial surface of, and blends with, the neuroma. The tumor is confined by the distended perineurial tube of the nerve of origin. It is composed of innervated primary units (fig. 202). The primary units are aggregated in broad interlacing fascicles. In the fascicles, nuclear palisades are often a feature (fig. 203). The endoneurial matrix is scanty and, in most examples, the fascicles are compactly aggregated. With a Bodian stain, numerous axons, some of which are mye-

Figure 200
NEUROMA

The solitary neuroma in the dermis is encapsulated. Closely aggregated tortuous fascicles of Schwann cells expand the perineurium. Hematoxylin and eosin stain.* X40.

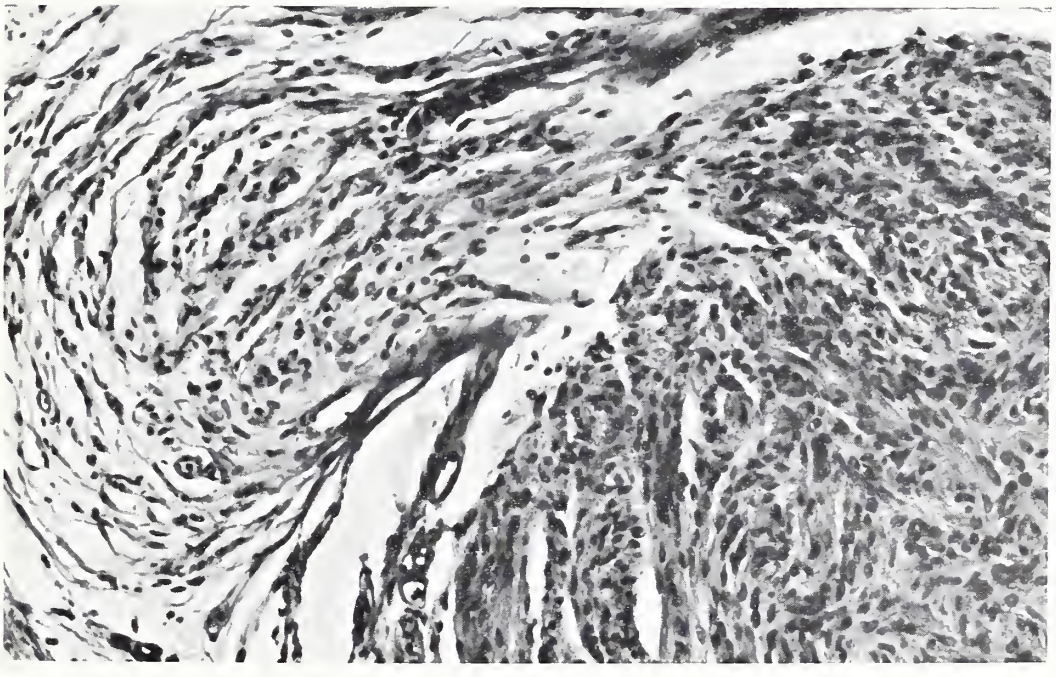

Figure 201
NEUROMA

A transition from the nerve of origin into a solitary encapsulated neuroma is illustrated. X250.

*Throughout the Supplement where the stain is not designated, the hematoxylin and eosin stain has been used.

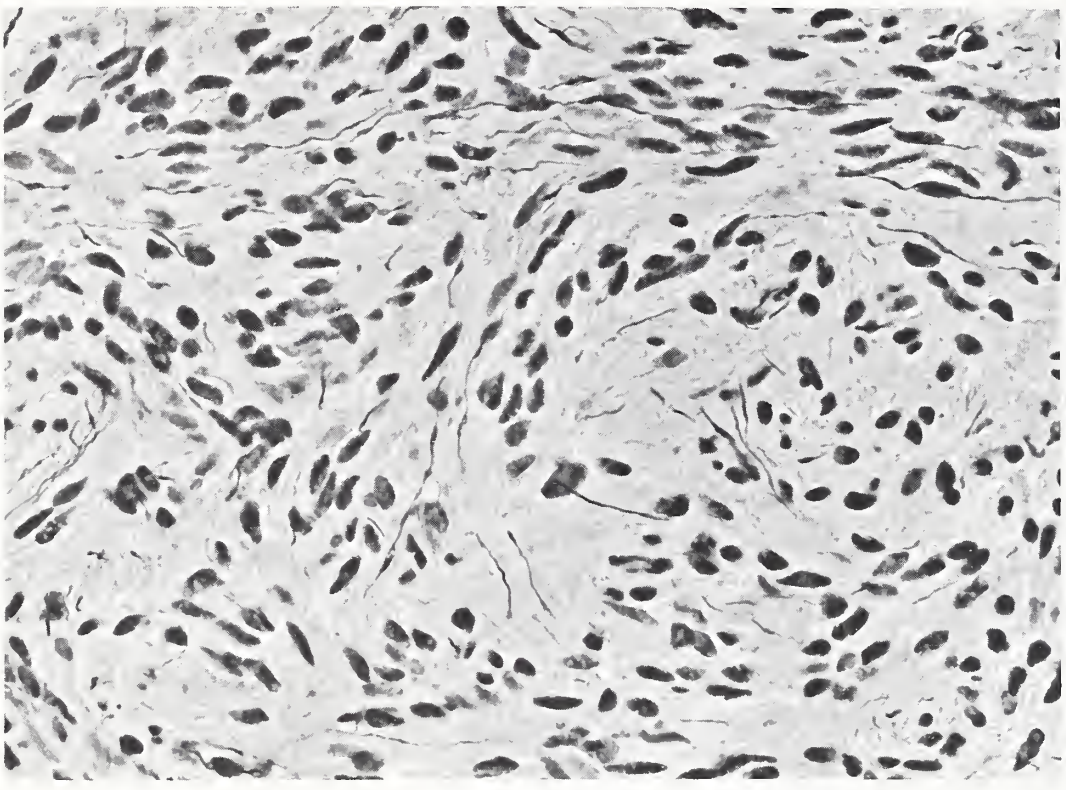

Figure 202
NEUROMA
The fascicles of sheath cells in this neuroma support argyrophilic axons. Bodian method. X400.

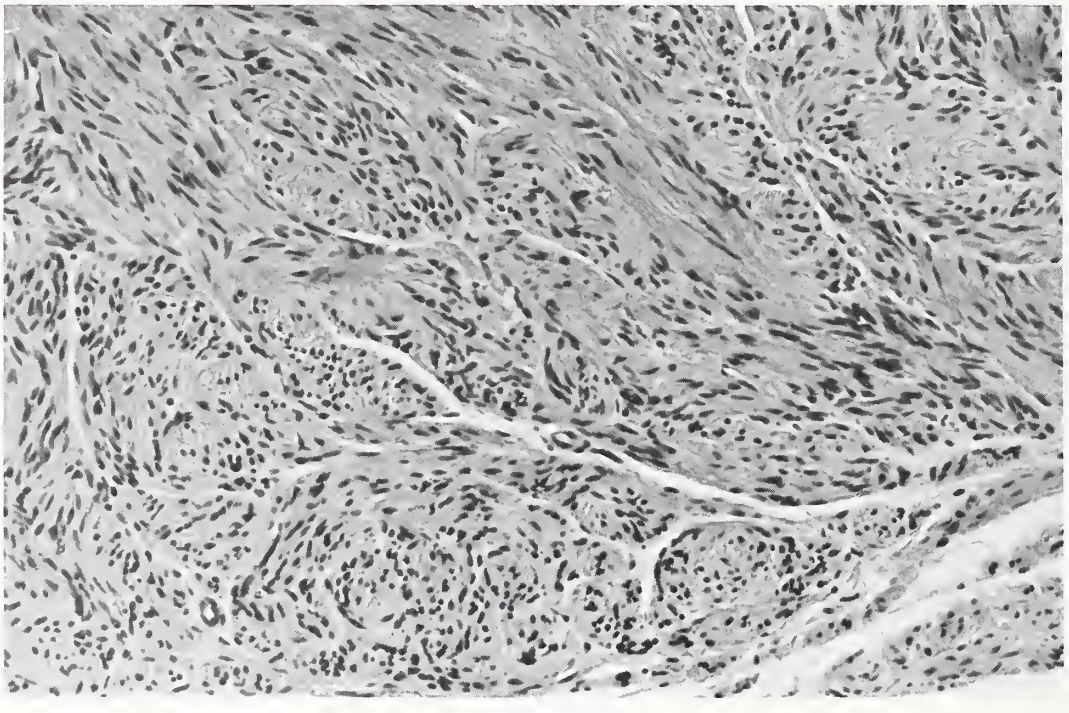

Figure 203
NEUROMA
In this solitary encapsulated neuroma, coarse fascicles intersect and are compactly aggregated. Intercellular fibrous matrix between neighboring fascicles is scanty. Nuclei in some fascicles form palisades. X250.

linated, are demonstrated in the fascicles (fig. 203).

In the mucosal neuroma syndrome, in addition to the localized neuromas, plexuses of nerve bundles are involved by the proliferative process (Williams and Pollock; Schitzler et al.; Bartley et al.). The primary units in the plexiform lesions form broad interlacing fascicles in the endoneurial space (fig. 100).

Variants

Rudimentary digit, amputation stump. Accessory digits may undergo spontaneous intrauterine autoamputation. A small fibrous protrusion marks the site of the autoamputation. Within the fibrous matrix, an infiltrating true neuroma resides (Shapiro et al.). Near the epidermis, in some examples, the nerve bundles terminate in numerous tactile corpuscles.

Pacinian neuroma. A pacinian neuroma is a tumorous hyperplasia of pacinian corpuscles (Schuler and Adamson). The pacinian corpuscle is a specialized end organ. A single axon terminates in a rounded aggregate of concentrically laminated perineurial cells (Weiser). In a pacinian neuroma, several pacinian corpuscles are closely clustered to form a localized tumor (fig. 204). Within the tumor, the individual corpuscles are relatively normal in size and structure. The lesion is often painful.

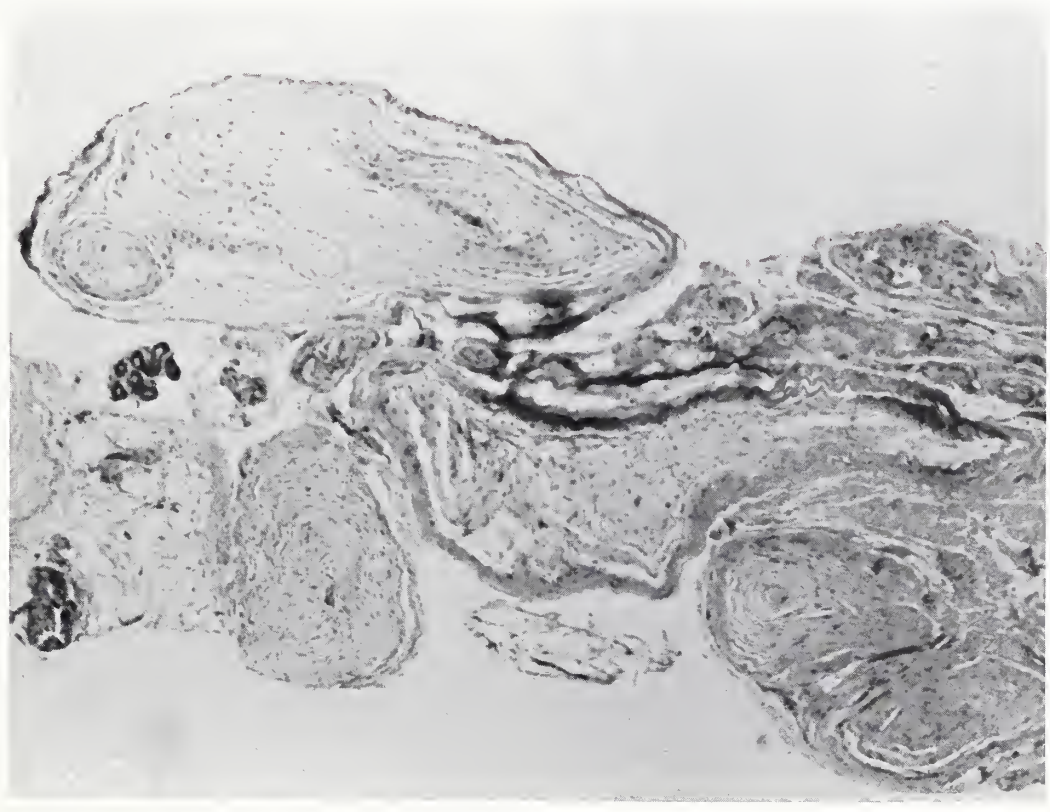

Figure 204
PACINIAN NEUROMA

This pacinian neuroma is composed of clusters of pacinian corpuscles. X25.

A pacinian neurofibroma is a rare tumorous hyperplasia of perineurial cells in a single pacinian corpuscle. The involved corpuscle is significantly enlarged. The concentric lamellae of perineurial cells are accentuated in number and also in the overall diameter of many of the lamellae.

Differential Diagnosis. Occasional small lesions of squamous mucous membranes show hypertrophied tortuous nerves in the lamina propria. The primary units in the nerves show concentric hyperplasia of Schwann cells. These variants of symmetrical neurofibromas are relatively common and may be confused with mucosal neuromas.

The dermal perineurial myxoma also has been classified as pacinian neurofibroma (MacDonald and Wilson-Jones).

References

Bartley, P. C., Lloyd, H. M., and Aitken, R. E. Medullary carcinoma of the thyroid, multiple phaeochromocytomas, mucosal neuromas, marfanoid habitus, and other abnormalities (Sipple's syndrome). Med. J. Aust. 2:173-176, 1976.

Dupré, A., Christol, B., Bonafé, J. L., Rumeau, H., Corberand, S., Bazez, J., and Lassere, J. Neurome cutané à tumeur unique avec importantes altérations des cellules schwanniennes. Ann. Dermatol. Syphiligr. 101:271-276, 1974.

MacDonald, D. M. and Wilson-Jones, E. Pacinian neurofibroma. Histopathol. 1:247-255, 1977.

Reed, R. J. Cutaneous manifestations of neural crest disorders (neurocristopathies). Int. J. Dermatol. 16:807-826, 1977.

_____, Fine, R. M., and Meltzer, H. D. Palisaded, encapsulated neuromas of the skin. Arch. Dermatol. 106:865-870, 1972.

Schitzler, L., Simard, C. L., Boudoux, C., and LeFrance, M. Neuromes cutanés et muquex avec étude histopathologique et ultrastructurale. Ann. Dermatol. Syphiligr. 100:241-260, 1973.

Schuler, F. A. III and Adamson, J. E. Pacinian neuroma, an unusual cause of finger pain. Plast. Reconstr. Surg. 62:576-579, 1978.

Shapiro, L., Juhlin, E. A., and Brownstein, M. H. Rudimentary polydactyly. Arch. Dermatol. 108:223-225, 1973.

Weiser, G. An electron microscope study of "pacinian neurofibroma." Virchows Arch. [Pathol. Anat.] 366:331-340, 1975.

Williams, E. D. and Pollock, D. J. Multiple mucosal neuromata with endocrine tumors. A syndrome allied to von Recklinghausen's disease. J. Pathol. 91:71-80, 1966.

BENIGN TUMORS OF NERVE SHEATH ORIGIN

SCHWANNOMA

In tumorous dysplasias of the neurosustentacular system, the neurosustentacular cells make variable contributions, but, in general, all the basic cells are represented. In neoplasms of the neurosustentacular system, a single type of neurosustentacular cell is usually involved and the tumors are expansile nodules.

Definition. The schwannoma is a benign expansile tumor of compactly aggregated sheath (Schwann) cells in a fibromyxomatous matrix (DasGupta et al.; Dahl). The lesion is confined by the perineurium and eccentrically compresses the primary units.

Histology. The tumor cells are anaxonal Schwann cells which form interlacing fascicles in an expansile nodule (Antoni A pattern; figs. 22, 23). The primary units of the nerve of origin are compressed eccentrically between the expanded perineurium and the tumor. The Schwann cells are elongated with complexly entangled processes (Erlandson and Woodruff). They are outlined ultrastructurally by continuous basal lamina (Lassmann et al.). Their tendency for longitudinal division finds expression in localized packets of cells and nuclear palisades. Two neighboring palisades of nuclei and the intervening cytoplasms comprise a Verocay body (fig. 29). Blood vessels are commonly grouped and ectatic. They often show thrombosis and subintimal deposits of fibrinoid (fig. 29). Some are microaneurysmal. In one or more foci, the Schwann cells acquire histiocytic (lytic) properties (Escalona-Zapata and Diez Nau; Sian and Ryan). In the expression of the lytic phase, lymphocytes and histiocytes are attracted to the areas of lysis (figs. 27, 28, 205). The lysis affects tumorous Schwann cells and mucinous matrix. As a result, portions of the tumor are converted to sparsely cellular areas in which delicate fascicles of Schwann cells and loosely aggregated, individual histiocytic Schwann cells are dispersed in a clear matrix (Antoni B pattern; fig. 27). The matrix is poor in acid mucopolysaccharides.

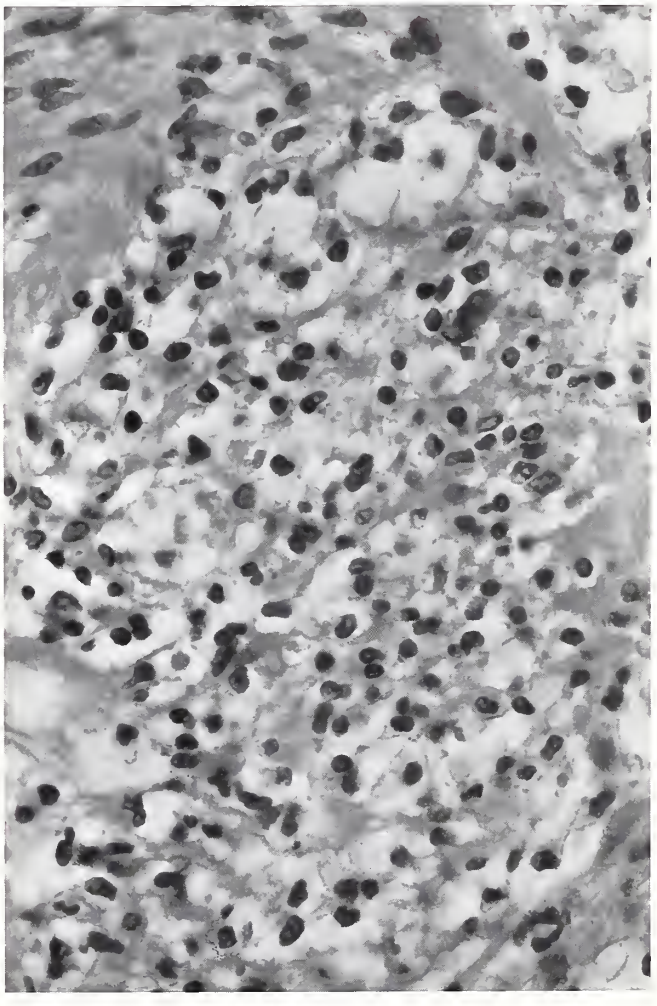

Figure 205
SCHWANNOMA
At the transition area between Antoni A and Antoni B tissue, the surviving delicate fascicles of sheath cells are associated with an infiltrate of lymphocytes and histiocytes. X400.

Histologic Variants. In some plexiform neurofibromas, multifocal nodules of compactly aggregated Schwann cells are irregularly distributed. They apparently have their origin from the primary units of the symmetrical axial bundle (fig. 206). These lesions may be the initial phase of a schwannoma arising in a neurofibroma or may express the initial phase of some plexiform schwannomas. They qualify as **neurofibroma** with **multifocal schwannomatosis.**

Occasional lesions are characterized by a diffuse endoneurial proliferation of Schwann cells in a plexiform pattern (**plexiform schwannoma**) (Masson; fig. 207). These lesions may represent an unusual complication in which multifocal schwannomatosis obliterates a parent neurofibroma. They may express an unusual propensity for a schwannoma to invade the endoneurial space. In two of our cases, a schwannoma with Antoni A and B patterns was found within the plexiform lesion. In some examples, plexiform schwannoma may express a transformation of a benign localized tumor to a locally infiltrating lesion. In one example, the fibrous

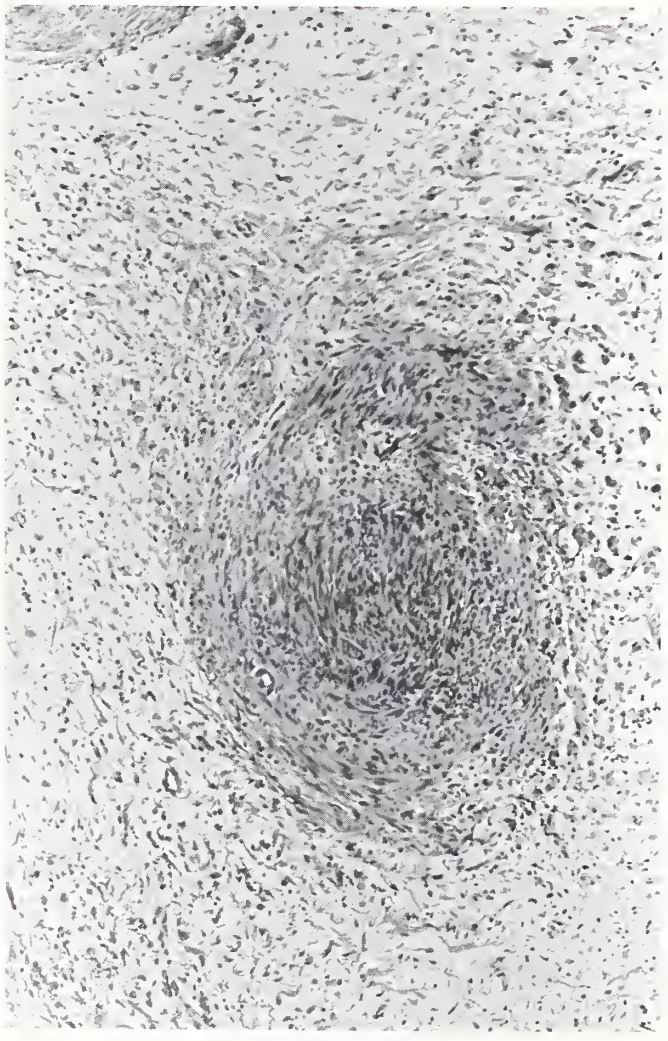

Figure 206
PLEXIFORM NEUROFIBROMA
The axial bundle in this plexiform neurofibroma is hypercellular. Closely aggregated Schwann cells form nuclear palisades and fascicles. X100.

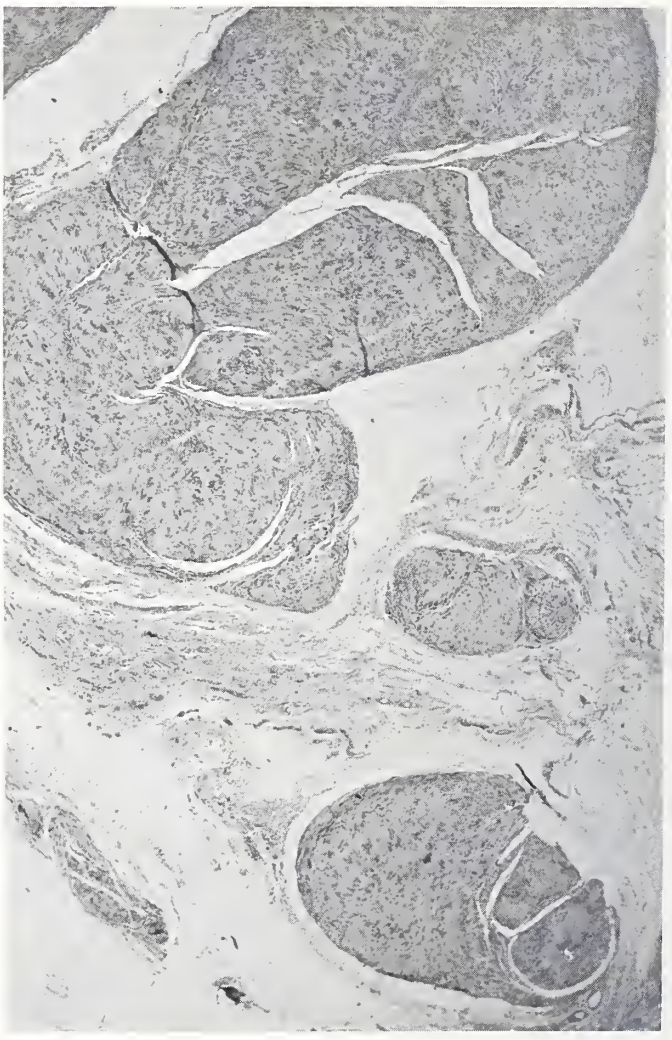

Figure 207
PLEXIFORM SCHWANNOMA
The plexiform qualities of this schwannoma are illustrated. X40.

tissue supporting the plexiform schwannoma contained tortuous, loosely aggregated fascicles of Schwann cells (fig. 208). The overall pattern in the fibrous tissue resembled a traumatic neuroma and, in areas, the fascicles were axonal. There is no explanation for a neuroma in the soft tissue supporting a plexiform schwannoma. The plexiform schwannoma may express an exaggerated potential for invasive growth by Schwann cells. Fascicles of Schwann cells may breach the perineurial sheath and impair its function as a diffusion barrier. A defective diffusion barrier may initiate the proliferation of axons and permit their growth along Schwann cell fascicles into the adjacent mesenchyme.

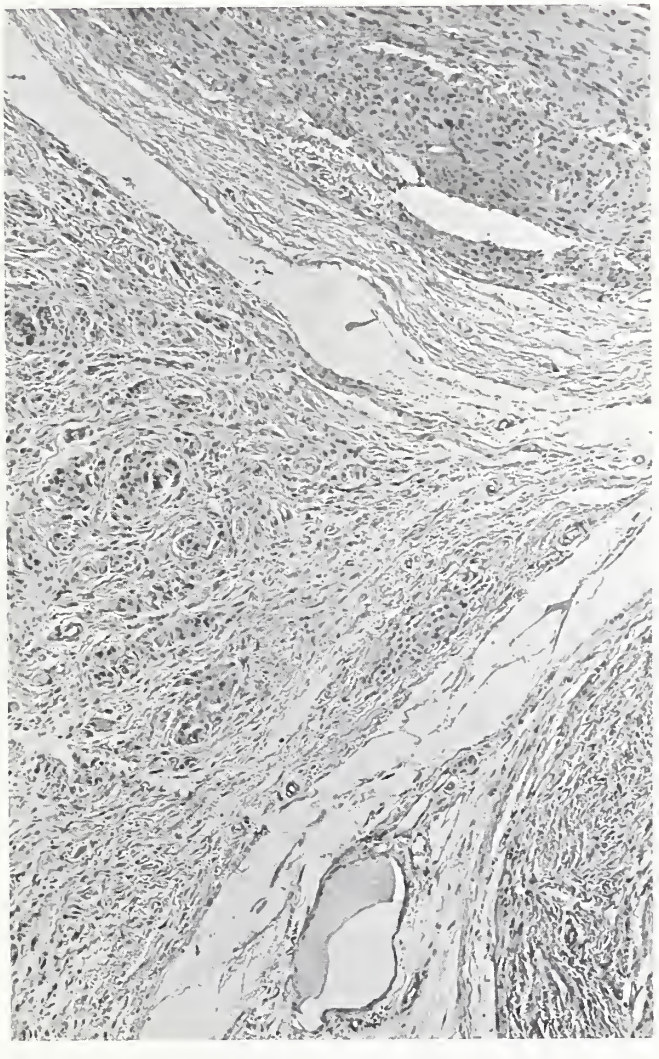

Figure 208
PLEXIFORM SCHWANNOMA
In this plexiform schwannoma, the adjacent mesenchyme contains tortuous fascicles of sheath cells in a neuromatous pattern. X100.

Schwannomas are occasionally multiple and disseminated. In this category, one example has shown, over a period of years, transformation of several schwannomas to minimally deviant malignant schwannomas. This variant apparently is familial.

In some schwannomas, the tumor cells are rounded and epithelioid (**epithelioid schwannoma**). The cells have hyperchromatic nuclei and a scanty to moderate amount of acidophilic cytoplasm (fig. 37). The epithelioid cells form Antoni A and B patterns. If nuclear atypism is prominent, the lesion may be mistaken for melanoma. The tumor cells in an epithelioid schwannoma do not contain melanin and do not show mitotic activity. In Antoni A zones, the epithelioid Schwann cells may form palisades at the periphery of islands of sclerotic fibrous tissue. In the islands, collagen fibers and cytoplasmic processes are radially arranged (fig. 30).

The lytic process which converts Antoni A to Antoni B tissue may result in focal areas of cystic degeneration (**cystic** or **multicystic schwannoma;** fig. 33). Occasionally, the cystic changes are extensive, with only scattered mural nubbins of surviving tumor.

In some schwannomas, the bulk of the tumor is composed of aneurysmally dilated vessels (**aneurysmal schwannoma**) (Kasantikul and Netsky). The vessels have thin walls and often contain organizing thrombi with the pattern of Masson's vegetative hemangioendothelioma. Such lesions are commonly misdiagnosed as a vascular malformation.

PERINEURIAL NEOPLASMS

Anatomy. The perineurial cell is an accepted component of peripheral nerves, but its relationship to the Schwann cell is unsettled. It is thin and has several rigid processes which attach to processes of neighboring perineurial cells. It differs from the Schwann cell in that it has no association with axons, its basal lamina is discontinuous, and its cytoplasm contains numerous micropinocytotic vesicles. In the inner layer of the perineurium, the perineurial cells form a continuous surface which has epithelial qualities. Its arrangement as a pavement, its tight intercellular junctions, and its pinocytotic functions contribute to a diffusion barrier between the epineurial and endoneurial tissues. The role of the perineurial cell in the maintenance of the endoneurial space has not been defined.

Occasionally, the Antoni A tissue of a schwannoma shows a peculiar mucinous transformation (figs. 31, 32). Plump cells (endoneurial mucocytes), with large, mucin-filled, cytoplasmic vacuoles, are loosely arranged in the mucinous areas (fig. 32). In the evolution of the mucinous pattern, the cytoplasmic vacuoles may open into the mucinous matrix (open configuration). In this manner, some of the cells acquire the morphologic features of perineurial cells and the cytoplasmic mucin becomes continuous with the extracellular matrix (see discussion of composite nerve sheath tumors). In their open configuration, they share morphologic features with the cells in a nerve sheath (perineurial) myxoma (pl. II-A in the Fascicle). The nature of the mucocyte involved in this peculiar transformation is uncertain. It is generally classified as a fibroblast, but similar cells in Morton's neuroma have perineurial qualities. In some schwannomas, the mucocyte appears to represent a peculiar transformation of Schwann cells in Antoni A tissue (fig. 32). It is also

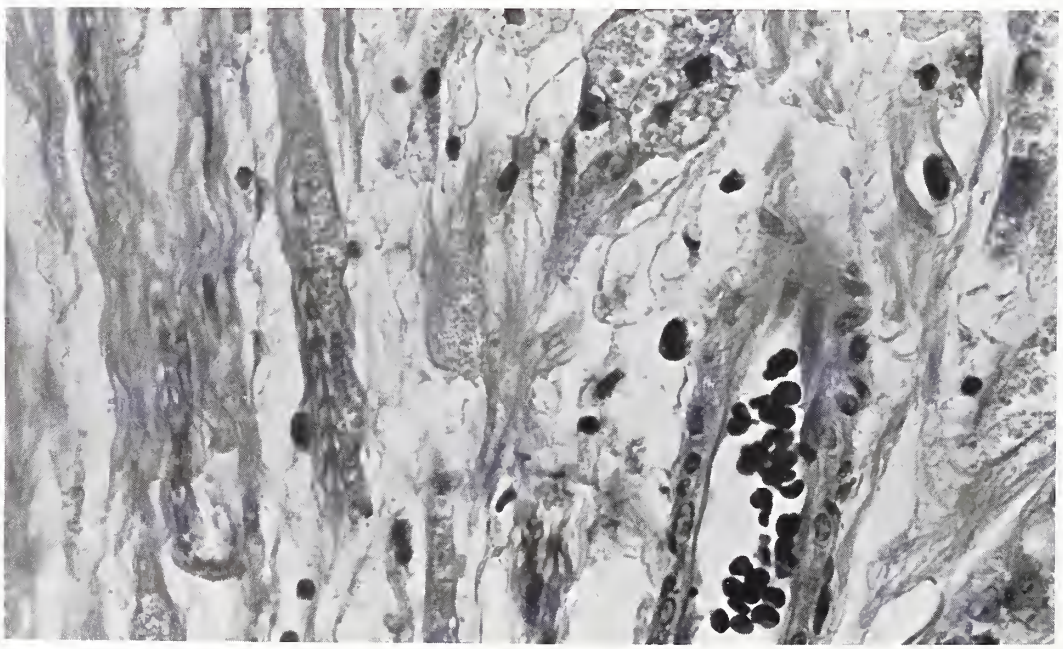

Figure 209
GRANULAR CELL SCHWANNOMA
In this granular cell schwannoma, continuity between innervated primary units and granular cells is documented. X400.

observed in some plexiform neurofibromas (figs. 52, 70). These peculiar mucocytes probably are a functional variant of neurosustentacular cells and may identify a transitional phase between Schwann cells and perineurial cells. By the latter concept, the Schwann cell and perineurial cell are functional variants of a single line of cells. When isolated in a mucinous endoneurial matrix, they qualify as endoneurial mucocytes. They correspond to the cellules godronné of Renaut and to the Krausenzellen of German pathologists.

The **granular cell tumor** remains controversial. For at least one variant, the component cells resemble phagocytic (histiocytic) Schwann cells, as seen in wallerian degeneration (Weiser; Sobel et al.; fig. 12). Some granular cell tumors form an expansile nodule in the endoneurial space, with compression of a portion of the nerve of origin and incorporation of axonal Schwann cell fascicles into the tumor (fig. 209). The fascicles lose their identity in the tumor. Some of the fascicles of granular cells infiltrate the perineurium. Such a lesion in a peripheral nerve clearly qualifies as a granular cell schwannoma. It has been proposed that some granular cell tumors are derived from perineurial cells.

The perineurial cells and their fibrous matrix form the perineurial tube. The perineurial cells form a continuous layer over specialized nerve endings: they are supporting cells for nerve endings in Meissner's and pacinian corpuscles. They are represented in some of the tactoid bodies in paraneurofibromas (figs. 81, 82). In fibrous plexiform neurofibromas, perineurial cells and their matrix obliterate the endoneurial space.

There are two tumors which qualify as perineurial neoplasms.

STORIFORM PERINEURIAL FIBROMA

Definition. The storiform perineurial fibroma is an expansile tumor that is composed of fibroblastic perineurial cells (Lazarus and Trombetta). It is confined by the perineurium and eccentrically displaces the nerve fibers. Perineurial fibromas are circumscribed fibrous tumors: they are the perineurial counterpart of schwannomas. Some of these lesions have true capsules (fig. 210).

Figure 210
STORIFORM PERINEURIAL FIBROMA
A condensation of fibrous tissue forms a capsule for this storiform perineurial fibroma. X250.

Histology. The perineurial fibroma occurs in either the skin or the soft tissues. Rarely, a polypoid perineurial fibroma forms a circumscribed tumor in the dermis. Perineurial fibromas are composed of spindle and stellate cells in a fasciculated

fibrous matrix (figs. 186, 187). At points of intersection, the fascicles produce starburst or storiform patterns (fig. 186). In some examples, the primary units of the nerve of origin can be identified eccentrically within the tumor. Ultrastructurally, the tumor cells have perineurial qualities. In the Fascicle, this lesion was classified as a storiform neurofibroma, but it is distinctly different from Bednar's storiform neurofibroma. The latter lesion is generally accepted as a pigmented dermatofibrosarcoma protuberans. Some examples in the soft tissue are not encapsulated. One recent example in the vagina was associated with stigmata of neurofibromatosis.

Differential Diagnosis. The perineurial fibroma shares its storiform pattern with dermatofibrosarcoma protuberans. The latter tumor is a fibrous plaque in the lower portion of the reticular dermis and the subcutaneous fat. It is an infiltrating tumor with ill-defined margins. In the evolution of dermatofibrosarcoma protuberans, one or several expansile nodules develop in the plaque. Melanocytes are an occasional component of dermatofibrosarcoma protuberans. They are an occasional feature of a perineurial fibroma in the dermis. Storiform perineurial fibromas are benign and seldom, if ever, recur following enucleation.

A storiform pattern is seen in perineurial fibromas and as a regional variation in some benign schwannomas (fig. 42) and in some malignant neuromesenchymomas (fig. 148). Its value as a marker for specific fibrohistiocytic tumors (i.e., fibrous histiocytomas) is questionable. The classification of a lesion as a fibrous histiocytoma does not define a cell of origin. Giant cell tumor of tendon sheath is a hyperplasia of fibrocytic and histiocytic synovial cells. Dermatofibrosarcoma protuberans is a low grade malignant dermal neuromesenchymoma. The cutaneous atypical fibrous xanthoma most commonly is an expression of a squamous cell carcinoma with sarcomatoid qualities.

PERINEURIAL MYXOMA (NERVE SHEATH MYXOMA)

Definition. The perineurial myxoma is a cutaneous tumor which is coarsely fasciculated and myxomatous. The fascicles vary in size and direction. The perineurial myxoma is primarily a tumor of the dermis. Mucinous changes are found in the perineurium of neighboring peripheral nerves. By the characteristics of its component cells, the nerve sheath myxoma (figs. 57–60) qualifies as a perineurial myxoma. The latter lesion has been classified also as a variant of a pacinian neurofibroma and as a bizarre myxoid neurofibroma (King and Barr).

Histology. In the dermis, the perineurial myxoma is composed of elongated spindle and stellate cells in a prominent mucinous matrix (figs. 58, 211). The cells have dense nuclear chromatin and elongated nuclei: their cytoplasm is acidophilic. The matrix contains acid mucopolysaccharides (pl. II-A in the Fascicle). On microscopic examination, the tumor appears multinodular and fasciculated (fig. 57). Some of the small nodules and fascicles are surrounded by condensations of fibrous tissue. In some of the larger nodules, the myxomatous matrix abuts upon the dermal connective tissue. In the nodules, the tumor cells are arranged in focal whorls which, in areas, remotely resemble the laminated perineurial cells of a pacinian corpuscle (fig. 57). Occasional examples are associated with a prominent infiltrate of

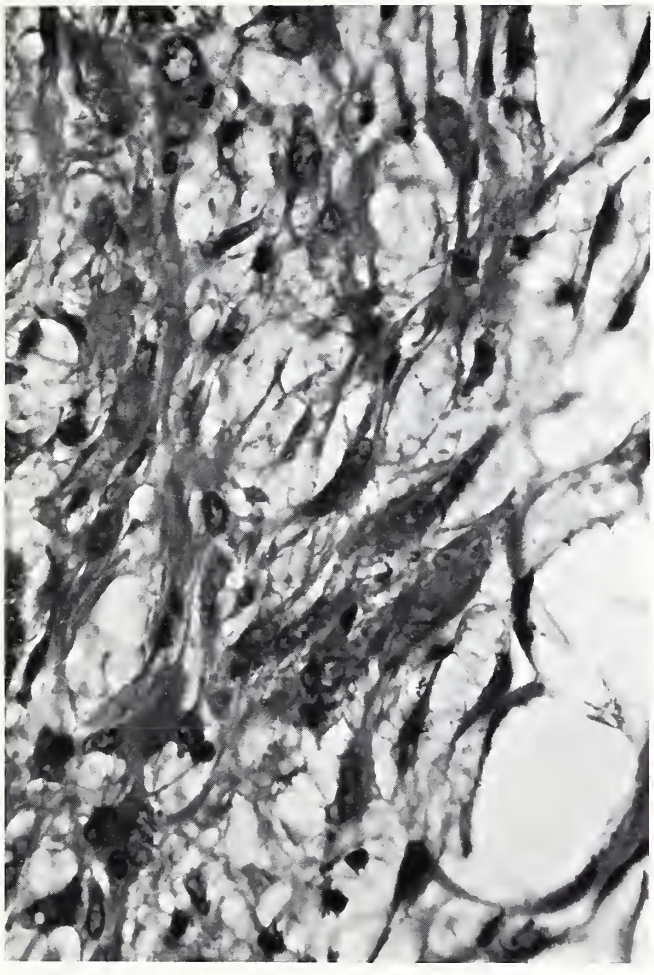

Figure 211
PERINEURIAL MYXOMA
In this perineurial myxoma, tumor cells have abundant cytoplasm and complex cytoplasmic processes. Nuclei are plump and show margination of chromatin. X400.

Figure 212
PERINEURIAL MYXOMA
As a regional variation, this perineurial myxoma is uniformly cellular. Even in the cellular portions, a mucinous matrix is present in the background between the tumor cells. X400.

lymphoid cells. Mitoses are not a reliable indicator of biologic behavior: in some examples, they are numerous. Cellular areas are prominent in some examples (figs. 60, 212). Even in the cellular zones, the tumor cells are supported by a myxomatous matrix. At the periphery of the tumor, small nerves occasionally show perineurial myxomatous hyperplasia. Ultrastructurally, the tumor cells have the characteristics of neurosustentacular cells (Sist and Greene).

Perineurial myxomas are benign, but occasionally produce local recurrences. There are rare examples in which cytologic atypism and mitotic activity qualify a lesion as atypical and borderline.

Composite nerve sheath tumors. The pattern of a nerve sheath myxoma is occasionally seen in tumors involving peripheral nerves in the deep soft tissues. In one example, schwannoma and nerve sheath myxoma were combined in a recurrent tumor (fig. 213). Such a lesion qualifies as a composite nerve sheath tumor. These composite tumors might also be cited as evidence supporting the mutability of Schwann cells and perineurial cells.

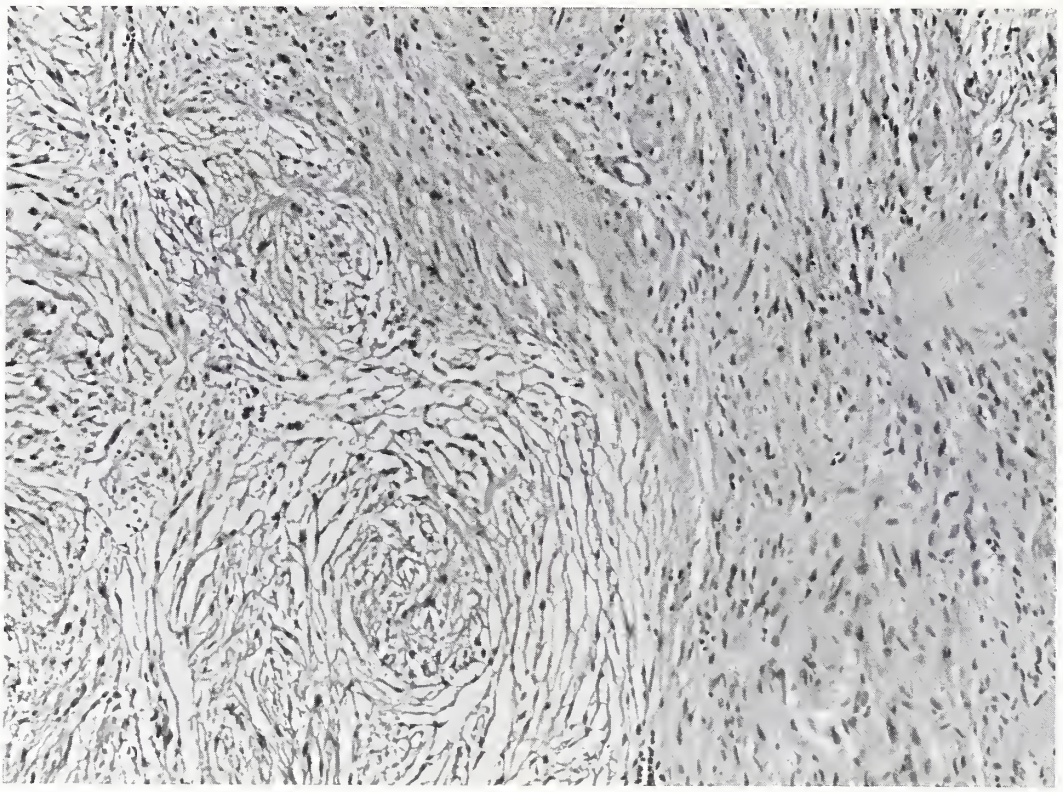

Figure 213
COMPOSITE SCHWANNOMA
In this composite schwannoma, there is a sharp interface between the myxoid perineurial component on the left and the Antoni A tissue on the right. X250.

References

Dahl, I. Ancient neurilemmoma (schwannoma). Acta Pathol. Microbiol. Scand. [A] 85A:812-818, 1977.

DasGupta, T. K., Brasfield, R. D., Strong, E. W., and Hajdu, S. I. Benign solitary schwannomas (neurilemomas). Cancer 24:355-366, 1969.

Erlandson, R. A. and Woodruff, J. M. Peripheral nerve sheath tumors. Cancer 49:273-287, 1982.

Escalona-Zapata, J. and Diez Nau, M. D. The nature of macrophages (foam cells) in neurinomas. Tissue culture study. Acta Neuropathol. 44:71-75, 1978.

Kasantikul, V. and Netsky, M. G. Combined neurilemmoma and angioma: Tumor of ectomesenchyme and a source of bleeding. J. Neurosurg. 50:81-87, 1979.

King, D. T. and Barr, R. J. Bizarre cutaneous neurofibromas. J. Cutan. Pathol. 7:21-31, 1980.

Lassmann, H., Jurecka, W., Lassmann, G., Gebhart, W., Matras, H., and Watzek, G. Different types of benign nerve sheath tumors. Virchows Arch. [Pathol. Anat.] 375:197-210, 1977.

Lazarus, S. S. and Trombetta L. D. Ultrastructural identification of a benign perineurial cell tumor. Cancer 41:1823-1829, 1978.

Masson, P. Human Tumors: Histology, Diagnosis, and Technique, pp. 1055, 1103, 1079-1086. 2d Ed. Translated by Kobernick S. D. Detroit: Wayne State Univ. Press, 1970.

Sian, C. S. and Ryan, S. F. The ultrastructure of neurilemoma with emphasis on Antoni B tissue. Hum. Pathol. 12:145-160, 1981.

Sist, T. C., Jr. and Greene, G. W., Jr. Benign nerve sheath myxoma. Oral Surg. 47:441-444, 1979.

Sobel, H. J., Marquet, E., and Schwarz, R. Is schwannoma related to granular cell myoblastoma? Arch. Pathol. 95:396-401, 1973.

Weiser, G. Granularzelltumor (granuläres neurom feyrter) und schwannsche phagen. Virchows Arch. [Pathol. Anat.] 380:49-57, 1978.

NEUROMESENCHYME

Definition. Neuromesenchyme is a conceptual component of mesenchyme (Reed, in press). It acquires distinguishing characteristics in tumorous dysplasias and loses its identity in nondescript mesenchymal patterns in adult tissues. Embryologically, a contribution from the neural crest to the cranial mesenchyme is accepted (LeLièvre and LeDouarin). The neuromesenchymal potential of neuroectoderm also finds expression in teratoid medulloblastomas and medulloepitheliomas (Lewis; Zimmerman et al.).

The differentiated cells which are derived from the neural crest (Weston) latently retain the potentials of their embryonic relatives. These differentiated cells include melanocytes, some mesenchymal cells, and neurosustentacular cells. In dysplasias, primary epigenic features and the latent potentials are variably expressed. The dysplastic cells express their potentials as a disorganized continuum: neurosustentacular cells may express melanogenic or mesenchymal properties. Melanogenic cells may express neurosustentacular or mesenchymal functions.

The melanocyte, the perineurial cell, and neuromesenchyme. The melanocyte is a neural crest derivative. Its migrations into the dermis in congenital and acquired hamartomas are usually interpreted as aimless. In the congenital nevus, melanocytes are distributed in files between collagen bundles (Mark et al.). The persistence of neurocristic cells (melanocytes) in dermal mesenchyme (reticular dermis) may express the defective incorporation of neurocristic effector cells into the target organ (skin: reticular dermis). On this basis, the migrations of melanocytes into the dermis in hamartomas become a grotesque recapitulation of the migration of neurocristic effector cells during embryogenesis (Reed, 1977). The dermis assumes the qualities of neuromesenchyme. The marker of a senescent nevus, the tactoid body, assumes the role of a marker for neuromesenchyme. In tactoid bodies and in Meissner's corpuscles, the sheath cells are perineurial cells (Weiser; Pease and Pallie). The perineurial cell and the melanocyte are mutable embryologic relatives and in neurocristic dysplasias either or both qualities may be expressed.

Neuromesenchyme and its tumorous dysplasias. The cutaneous neurofibroma is an extraperineurial lesion. It is a hyperplasia of neuromesenchyme around the open end of a peripheral nerve (Reed, in press). It adapts to a defect in dermal mesenchyme and supports appendages that are regularly spaced. The appendages are not compressed or displaced by the dermal tumor (fig. 55). The cutaneous neurofibroma is a hamartomatous expression of dermal neuromesenchyme.

The extraperineurial component (so-called diffuse or paraneurofibromatous component) of a plexiform neurofibroma commonly shows admixtures of neuromesenchyme and lipocytes (Reed, in press; fig. 78). The fibrous neuromesenchyme supports and intermingles with lipocytes. The extraperineurial component often contains tactoid bodies (figs. 81, 82) and melanocytes (fig. 214), two components that have the qualities of markers for neuromesenchyme (Reed, in press).

The mesenchymal qualities of some examples of neurofibromatosis are illustrated

in the associated vascular lesions (Feyrter; Greene et al.; Salyer and Salyer; Reyes et al.; Tilford and Kelsch; Brunner et al.; Schubiger and Yasargil). The latter are recognized associations in neurofibromatosis and may be related to an endothelial proliferative factor (Suddith et al.). The abdominal aorta and its branches are most commonly involved, but lesions have been described in the heart, carotid artery, and vertebral artery. Involvement of the kidney and coarctation of the aorta are associated with hypertension. Other complications include aneurysms with rupture and hemorrhage. The vascular lesions may be either an isolated manifestation or associated with a neurofibroma (aneurysmal neurofibroma). Greene and associates propose a separation between the lesions of large vessels that are intimately associated with a neurofibroma and the isolated lesions of small vessels. The latter in the kidney may be extensive and multifocal. Their distribution may seriously compromise surgical attempts to correct the associated renovascular hypertension.

Four variants of angiomatous malformations have been described (Salyer and Salyer):

1. pure intimal
2. intimal—aneurysmal
3. periarterial nodular
4. advanced intimal and epithelioid

Histologically, the vascular lesions are characterized by intimal hyperplasias, fragmentation or absence of the internal elastica lamina, fibrous defects in the media, and fibrous hyperplasia of the

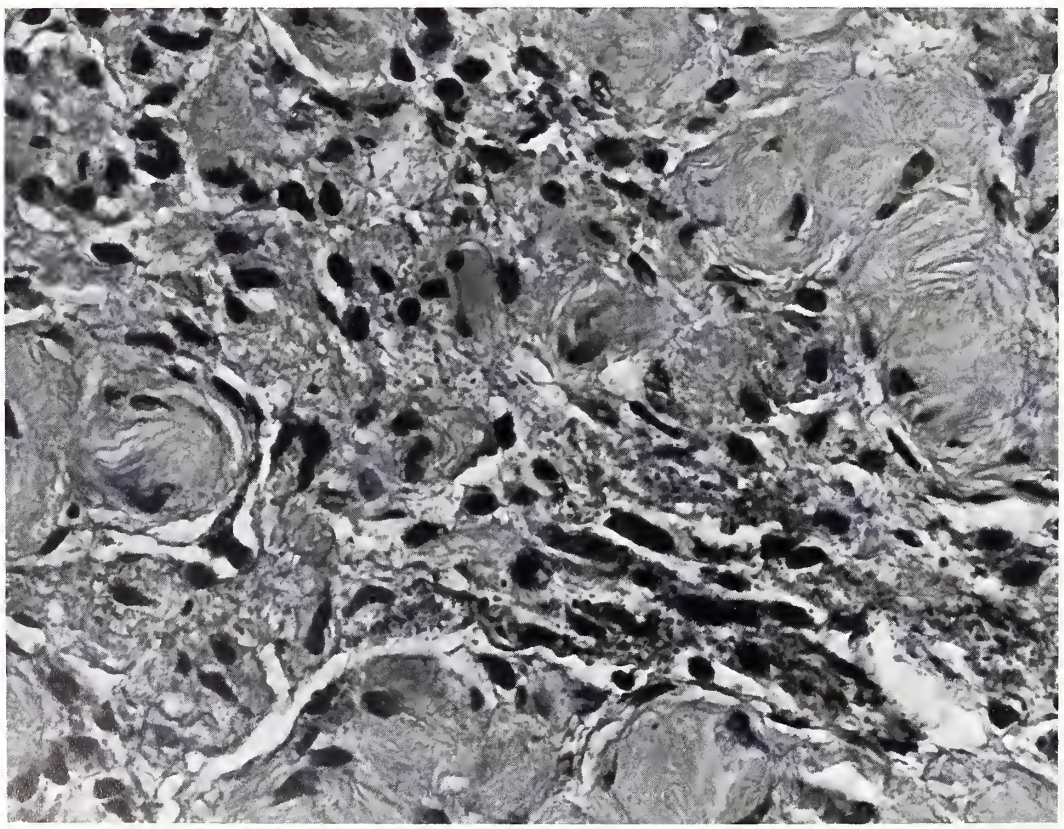

Figure 214
PARANEUROFIBROMA
Tactoid bodies and pigmented melanocytes are clustered in this area of a paraneurofibroma. X400.

adventitia. In the small vessels, widely scattered nodules of smooth muscle are characteristic.

Summary. The dermis qualifies as neuromesenchyme. The extraepithelial melanocyte and the tactoid body are markers for neuromesenchyme in neuroectodermal hamartomas (fig. 214). An expression of neuromesenchyme is found in histologic patterns in most malignant plexiform neurofibromas: most examples of the latter process qualify as malignant neuromesenchymomas (Reed, in press). Their mesenchymal qualities are expressed in patterns which resemble fetal mesenchyme, including chondroid, rhabdomyomatous, and lipomatous differentiation.

References

Brunner, H., Stacher, G., Bankl, H., and Grabner, G. Chronic mesenteric arterial insufficiency caused by vascular neurofibromatosis. Am. J. Gastroenterol. 62:442-447, 1974.

Feyrter, F., Über die vasculäre neurofibromatose, nach Untersuchungen am menschlichen Magen-Dermschlauch. Virchows Arch. [Pathol. Anat.] 317:221-265, 1949.

Greene, J. F., Jr., Fitzwater, J. E., and Burgess, J. Arterial lesions associated with neurofibromatosis. Am. J. Clin. Pathol. 62:481-487, 1974.

LeLièvre, C. S. and LeDouarin, N. M. Mesenchymal derivatives of the neural crest: Analysis of chimaeric quail and chick embryos. J. Embryol. Exp. Morphol. 34:125-154, 1975.

Lewis, A. J. Medulloblastoma with striated muscle fibers. J. Neurosurg. 38:642-646, 1973.

Mark, G. J., Mihm, M. C., Liteplo, M. G., Reed, R. J., and Clark W. H. Congenital melanocytic nevi of the small and garment type. Hum. Pathol. 4:395-418, 1973.

Pease, D. C. and Pallie, W. Electron microscopy of digital tactile corpuscles and small cutaneous nerves. J. Ultrastruct. Res. 2:352-365, 1959.

Reed, R. J. Cutaneous manifestations of neural crest disorders (neurocristopathies). Int. J. Dermatol. 16:807-826, 1977.

———. Neuromesenchyme: The concept of a neurocristic effector cell for dermal mesenchyme. Am. J. Dermatopathol. (In press).

Reyes, J. M., Putong, P. B., Vangore, S., and Stein, B. Retroperitoneal neurofibromatosis and venous anomalies. Arch. Pathol. Lab. Med. 104:646-648, 1980.

Salyer, W. R. and Salyer, D. C. The vascular lesions of neurofibromatosis. Angiology 25:510-519, 1974.

Schubiger, O. and Yasargil, M. G. Extracranial vertebral aneurysm with neurofibromatosis. Neuroradiol. 15:171-173, 1978.

Suddith, R. L., Kelly, P. J., Hutchison, H. T., Murray, E. A., and Haber, B. In vitro demonstration of an endothelial proliferative factor produced by neural cell lines. Science 190:682-684, 1975.

Tilford, D. L. and Kelsch, R. C. Renal artery stenosis in childhood neurofibromatosis. Am. J. Dis. Child. 126:665-668, 1973.

Weiser, G. Neurofibrom und perineuralizelle. Virchows Arch. [Pathol. Anat.] 379:73-83, 1978.

Weston, J. A. The Regulation of Normal and Abnormal Neural Crest Cell Development, pp. 77-95. In: Advances in Neurology, Vol. 29, Neurofibromatosis. Riccardi, V. M. and Mulvihill, J. J. (Eds.). New York: Raven Press, 1981.

Zimmerman, L. E., Font, R. L., and Anderson, S. R. Rhabdomyosarcomatous differentiation in malignant intraocular medulloepitheliomas. Cancer 30:817-835, 1972.

TUMOROUS DYSPLASIAS OF THE NEUROSUSTENTACULAR SYSTEM

CIRCUMSCRIBED NEUROFIBROMA

Definition. A circumscribed neurofibroma is a circumscribed hamartomatous distortion of the supporting tissue (neurosustentacular system) of a peripheral nerve or plexus of nerves (Lassmann et al., 1977b). Its confines with adjacent normal mesenchyme are delimited by the perineurium. It recapitulates in an abnormal fashion the neurosustentacular components of a normal peripheral nerve. Tortuous (asymmetrical) Schwann cell fascicles are relatively anaxonal and fibrous (fig. 83). The endoneurial matrix is expanded and cellular. The perineurium is hyperplastic (figs. 74, 77) and makes a variable contribution to the endoneurial space, occasionally obliterating it (figs. 215, 216). It defines the limits of a circumscribed neurofibroma. In some examples, a symmetrical or axial bundle of axonal sheath cells is represented (Masson; figs. 68, 71). Rarely, pigmented melanocytes are found in the endoneurial matrix (fig. 217). Ultrastructurally, collagen fibrils have a diameter of 400-500 Å: they are comparable to collagen fibrils of the endoneurial type (Lassmann et al., 1975).

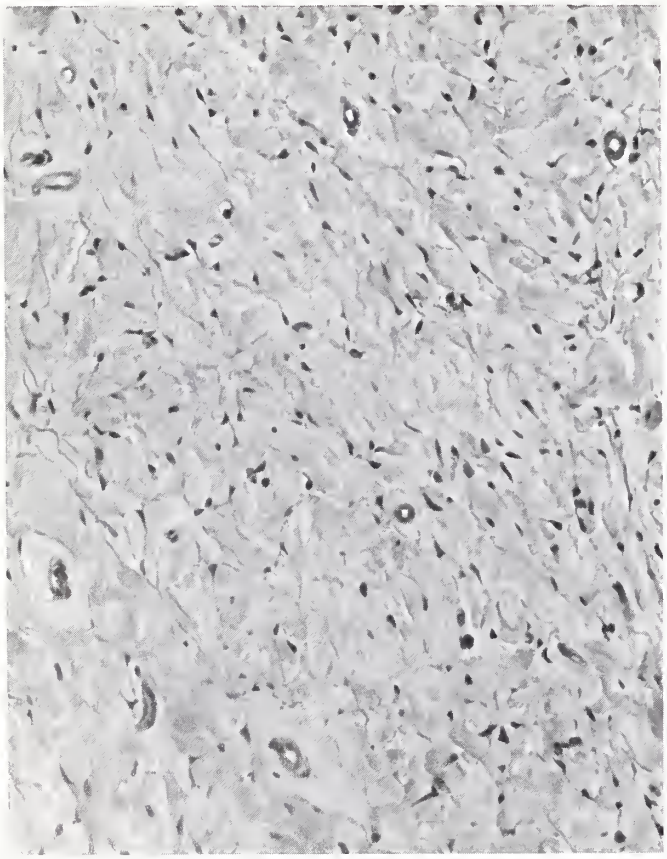

Figure 215
PLEXIFORM NEUROFIBROMA
This plexiform neurofibroma is uniformly fibrous. The supporting cells have perineurial qualities. X100.

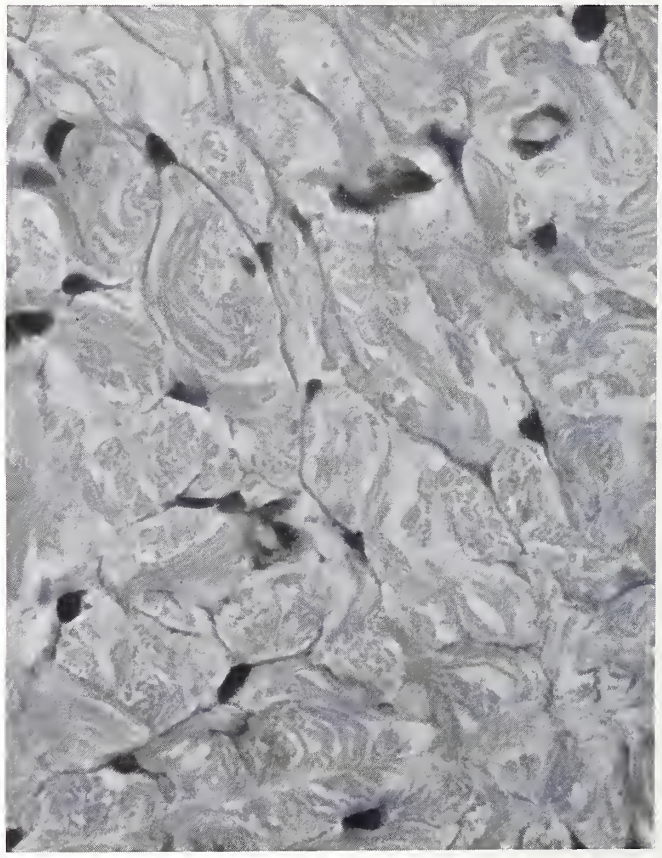

Figure 216
PLEXIFORM NEUROFIBROMA
The perineurial qualities of the supporting cells in this fibrous plexiform neurofibroma are illustrated. X400.

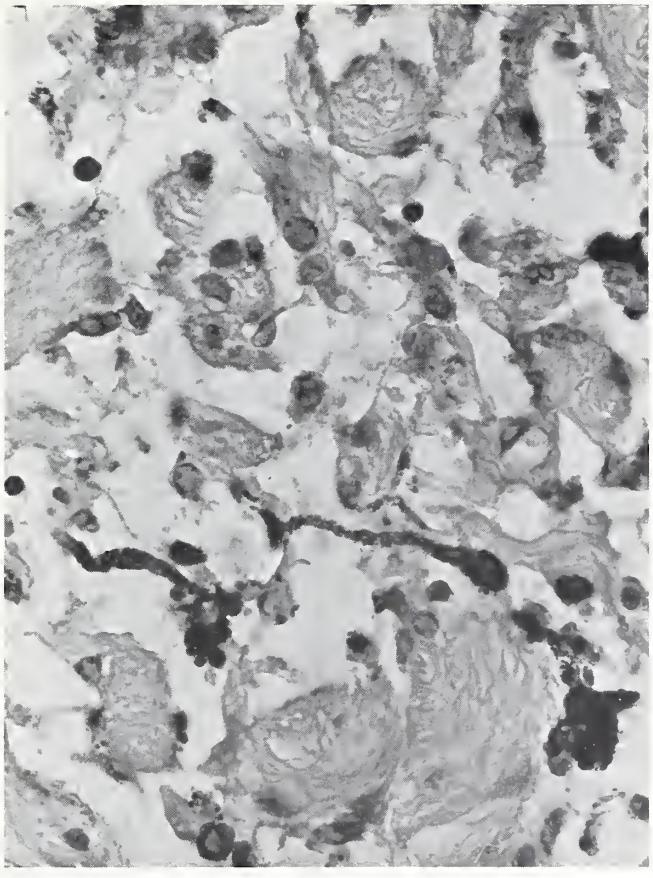

Figure 217
PLEXIFORM NEUROFIBROMA
Pigmented dendritic melanocytes are present in the endoneurial matrix of this plexiform neurofibroma. X400.

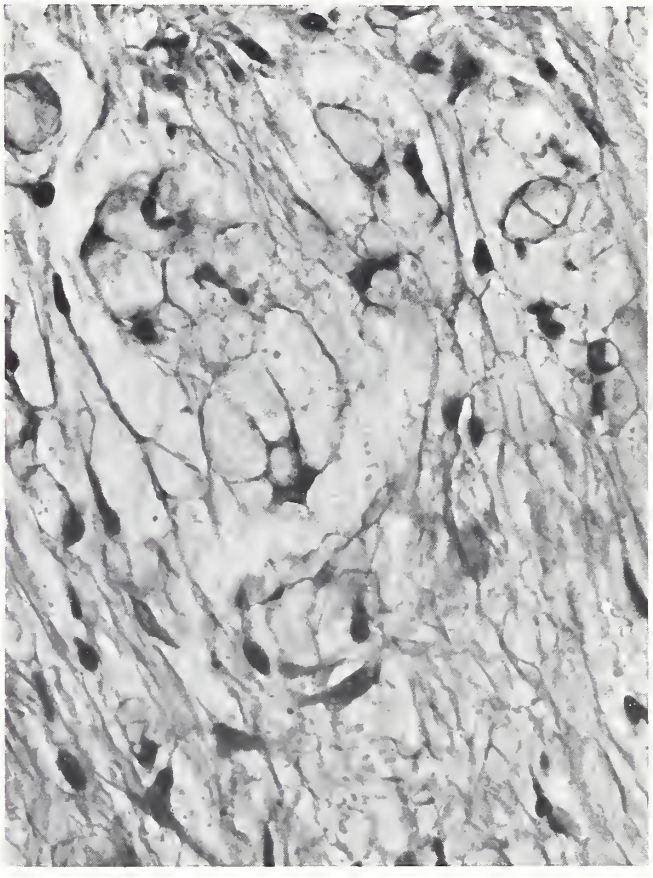

Figure 218
PLEXIFORM NEUROFIBROMA
As a regional variation in pattern, this plexiform neurofibroma is mucinous. Cells with perineurial qualities encircle and entrap the mucinous matrix. X400.

Variants

In a circumscribed plexiform neurofibroma, the representation of fibrous Schwann cell fascicles, endoneurial matrix, and perineurium is variable. In some examples, proliferating perineurial cells extend into the endoneurial matrix. They are associated with a dense fibrous matrix which resembles the perineurium. Eventually, the nerve is converted to a fibrous cord in which a symmetrical bundle of axonal Schwann cell fascicles may be preserved. These variants qualify as **fibrous plexiform neurofibromas** (perineurial dominance; figs. 74, 215).

In some neurofibromas, the endoneurial matrix is abundant and mucinous. Focally, the mucinous endoneurial matrix in a plexiform neurofibroma may obscure the Schwann cell component (fig. 218). In some mucinous variants, peculiar, large epithelioid cells with multiple mucin-filled cytoplasmic vacuoles are loosely arranged in the matrix (fig. 218). They are usually classified as fibroblasts and qualify as altered endoneurial cells. These lesions qualify as **mucinous plexiform neurofibromas** (endoneurial dominance; figs. 69, 76). The cells in some neurofibromas are argyrophilic: this property apparently reflects a functional state of the tumor cells (Lassmann et al., 1975).

PARANEUROFIBROMA (DIFFUSE NEUROFIBROMA)

Definition. A paraneurofibroma is an extension beyond the confines of the perineurium of neuromesenchyme and its specialized supporting cells (figs. 75, 78; Reed, in press). It contains small neurofibromatous nerves and may contain tactoid bodies (Schochet and Barrett; figs. 81, 82) and melanocytes (Dible; figs. 105, 214). It often supports a circumscribed plexiform component (fig. 75). It is a delicate fibrous matrix containing spindle cells (Schwann cells and fibrocytes). Lipocytes are often clustered in foci within the tumor (fig. 78). The margins with normal tissue are ill-defined. A diffuse neurofibroma fills a defect in mesenchyme. In some examples, the tactoid bodies are composed of Schwann cells rather than perineurial cells (Lassmann et al. 1977a,b).

In an **aneurysmal paraneurofibroma,** vessels are numerous and some are aneurysmal (Berggren et al.; Hruban et al.). The vessels are a component of the paraneurofibroma. Their muscular walls are irregular. In some examples, tactoid bodies are closely aggregated in the walls of the dilated vessels (figs. 219, 220). In the large aneurysms, the walls often are composed of organizing granulation tissue. In our material, the parotid gland is a favored site for an aneurysmal paraneurofibroma.

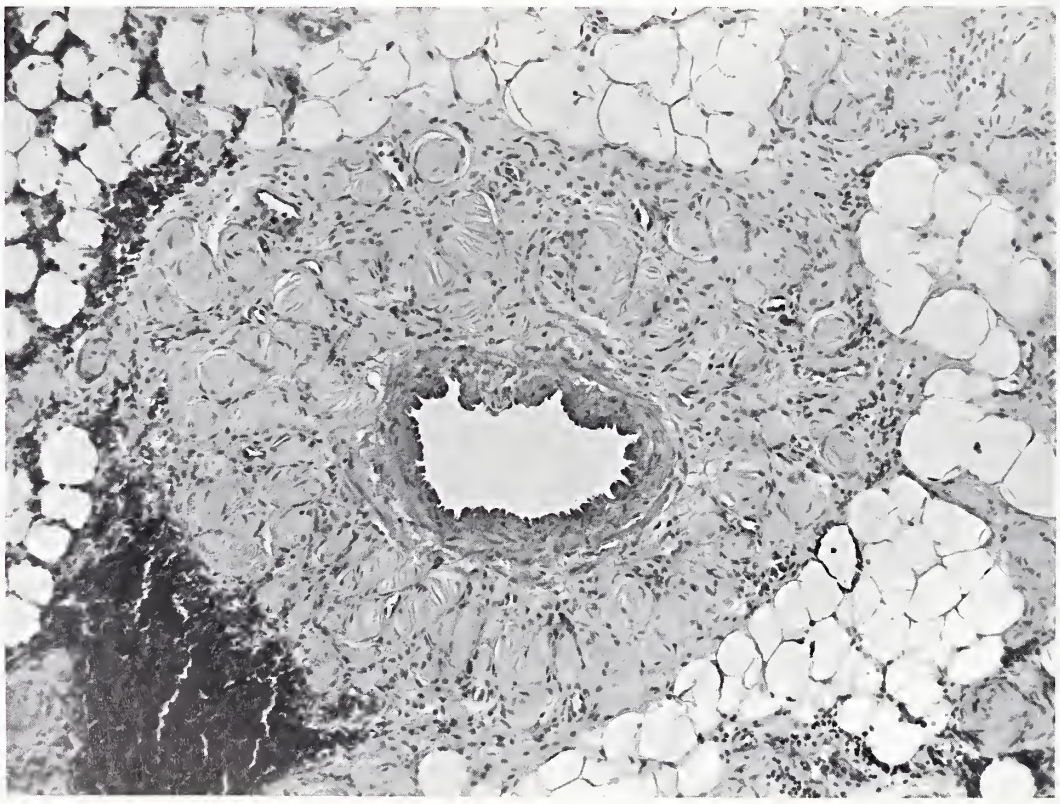

Figure 219
PARANEUROFIBROMA
In this paraneurofibroma, adipose tissue and clusters of tactoid bodies are admixed. Tactoid bodies have concentrated in the adventitia of a muscular vessel. X60.

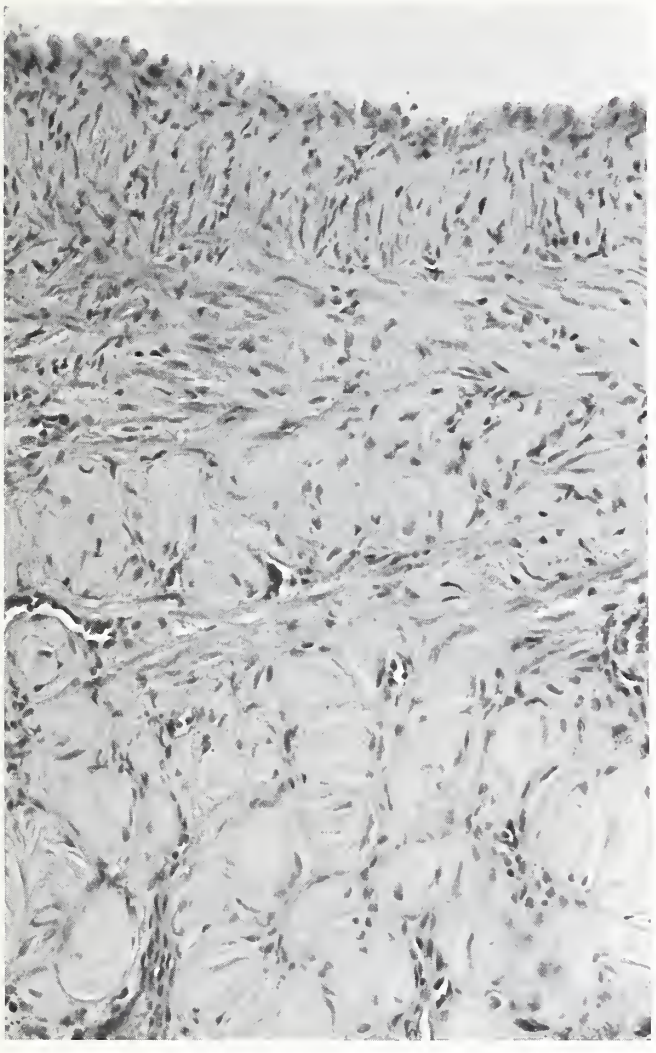

Figure 220
ANEURYSMAL NEUROFIBROMA
In this aneurysmal neurofibroma, the wall of a dilated vessel contains clusters of tactoid bodies. X250.

PLEXIFORM EPITHELIOID NEUROFIBROMA

Definition. The plexiform epithelioid neurofibroma is a rare plexiform tumor composed of plump rounded epithelioid cells with Schwann cell qualities. A paraneurofibroma may support the plexiform component. The tumor cells often form rigid fascicles (fig. 115) which are outlined by reticular fibers and PAS positive basement membranes. Nuclear atypism, with variations in size and with hyperchromatism, is prominent (figs. 112-114). The paraneurofibromatous component is an aid in diagnosis (figs. 104, 105). It may contain pigmented melanocytes and tactoid bodies (fig. 105). The scalp is apparently a favored site. In one example, in a child, an undifferentiated small cell neuroectodermal tumor of the cerebellum (fig. 116) was the cause of death, although the tumor of the scalp was recurrent and locally aggressive. In its propensity for local recurrence, the epithelioid neurofibroma may represent a minimal deviation malignant neurofibroma. Occasional malignant schwannomas have similar epithelioid qualities (fig. 140).

SYMMETRICAL NEUROFIBROMA

Definition. A symmetrical neurofibroma is a tumorous hyperplasia in which neurosustentacular cells form concentric lamellae around preserved myelinated axons (Masson). Concentric hyperplasia of neurosustentacular cells characterizes the response in hypertrophic interstitial neuritis. Rare isolated tumors show the pattern of symmetrical hyperplasia of neurosustentacular cells. The concentric lamellae are oriented in a symmetrical fashion around primary units along the long axis of the nerve of origin. This pattern may be seen in neurofibromas near the nerve roots, and is also seen in symmetrical neurofibromas of the extremities. The nature of this lesion is controversial (Weller and Cervós-Navarro). Similar lesions are reported as either neoplasms or as traumatic in origin.

Grossly, the lesion is indistinguishable from a circumscribed plexiform neurofibroma.

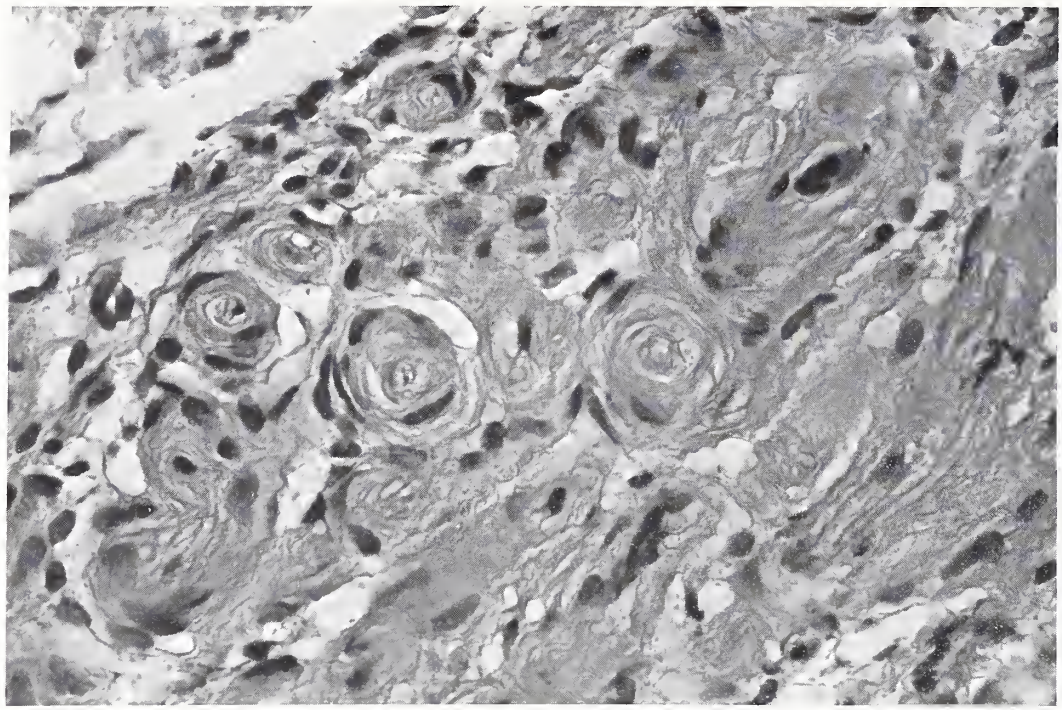

Figure 221
SYMMETRICAL NEUROFIBROMA
In this symmetrical neurofibroma, Schwann cells form concentric lamellae around primary units. Some of the primary units are cut in longitudinal section. X400.

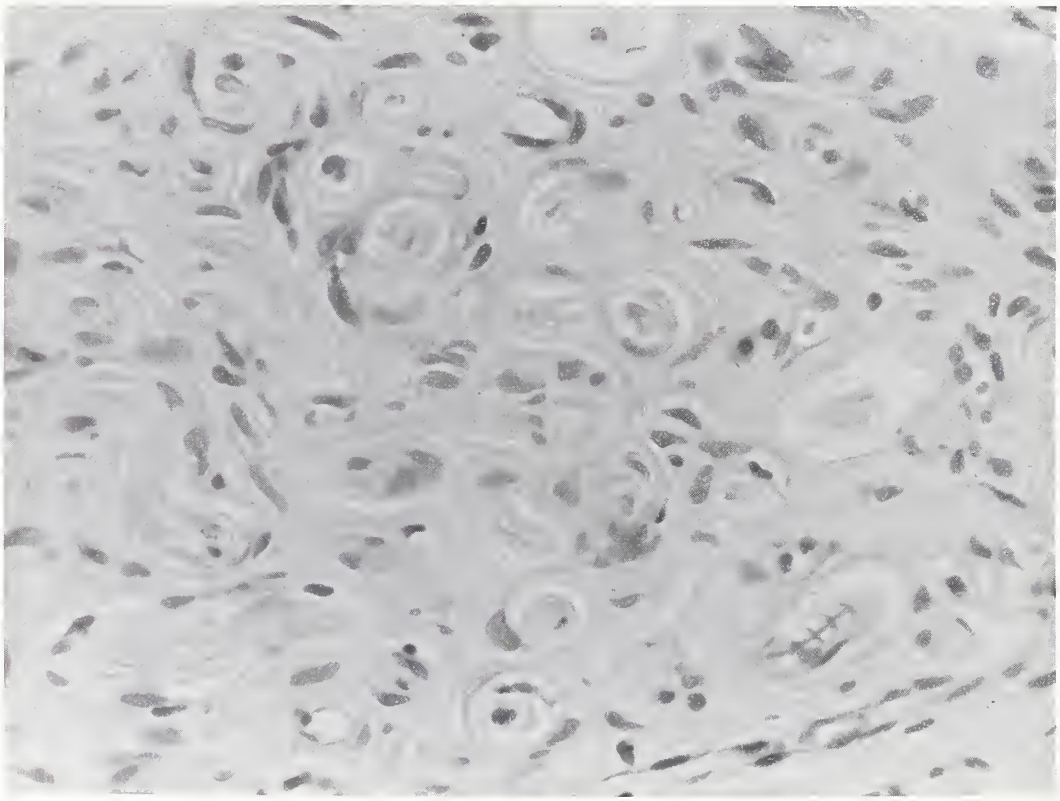

Figure 222
SYMMETRICAL NEUROFIBROMA
The concentric hyperplasia of sheath cells in this peripheral nerve characterize the neural changes in localized gigantism. X250.

Histology. The involved nerves are coarsened and tortuous. The perineurium is hyperplastic and fibrous. In cross section, the myelinated fibers are widely spaced in a fibrous endoneurial matrix and are outlined by concentric lamellae of plump spindle cells (figs. 99, 221). The lamellae are loosely aggregated. The concentric lamellae surround an axon. In most examples, the axons are myelinated, but focally the axons degenerate and the lamellae are fibrous.

In localized gigantism, small nerves in the excess tissue show concentric hyperplasia of Schwann cells in the pattern of a symmetrical neurofibroma (Lassmann et al., 1977a; fig. 222). Small symmetrical neurofibromas are occasionally an incidental finding on mucous membranes of the oral cavity and upper respiratory tract.

References

Berggren, R. B., Mohler, L. R., and Ferraro, J. W. Excision of massive hemangioneurofibroma of the face. Plast. Reconstr. Surg. 58:444-449, 1976.

Dible, J. H. Verocay bodies and pseudomeissnerian corpuscles. J. Pathol. Bacteriol. 85:425-433, 1963.

Hruban, Z., Evans, R. W., and Humphreys, E. M. An unusual form of neurovascular hamartoma. Arch. Pathol. 69:672-682, 1960.

Lassmann, H., Gebhart, W., and Stockinger, L. The reaction of connective tissue fibers in the tumor of Recklinghausen's disease. Virchows Arch. [Cell Pathol.] 19:167-177, 1975.

———, Gebhart, W., Mamoli, B., and Niebauer, G. Nervous lesions in a case of local gigantism. Acta Neuropathol. 38:109-115, 1977a.

———, Jurecka, W., Lassmann, G., Gebhart, W., Matras, H., and Watzek, G. Different types of benign nerve sheath tumors. Virchows Arch. [Pathol. Anat.] 375:197-210, 1977b.

Masson, P. Human Tumors: Histology, Diagnosis, and Technique, pp. 1055, 1103, 1079-1086, 2d Ed. Translated by Kobernick, S. D. Detroit: Wayne State Univ. Press, 1970.

Reed, R. J. Cutaneous manifestations of neural crest disorders (neurocristopathies). Int. J. Dermatol. 16:807-826, 1977.

———. The Neural Crest, its Migrants and Cutaneous Malignant Neoplasms Related to Neurocristic Derivatives in Cancer-Associated Genodermatoses. Lynch, H. T. (Ed.). New York: Van Nostrand Reinhold Co. (In press).

Schochet, S. S., Jr. and Barrett, D. A. II. Neurofibroma with aberrant tactile corpuscles. Acta Neuropathol. 28:161-165, 1974.

Weller, R. O. and Cervós-Navarro, J. Pathology of Peripheral Nerves, pp. 150-152. London: Butterworth & Co., Ltd., 1977.

PRIMARY MALIGNANT TUMORS OF NERVES AND NERVE SHEATHS

Nomenclature. The term malignant schwannoma embraces most of the primary malignant tumors of peripheral nerves and, additionally, incriminates the Schwann cell as the progenitor. Ultrastructurally, the tumor cells may have the qualities of Schwann cells (Taxy et al; Woodruff et al., 1981). In some examples, they have complex intertwining cytoplasmic processes and cytoplasmic fibrils. In the general category of malignant schwannomas, the variable histologic patterns may include specific mesenchymal components.

A classification of malignant tumors of nerve sheaths should identify benign precursors and distinguish the transformed lesions from their de novo counterparts. It should give recognition to distinctive histologic patterns and clearly distinguish lesions with mesenchymal qualities from a second major category, in which tumor cells are epithelioid. It should, additionally, give recognition to rare qualities, such as glandular patterns in teratoid variants.

Of the current classifications, few, if any, embrace all of the variables (D'Agostino et al., 1963a,b; Russell and Rubinstein; DasGupta and Brasfield; Ghosh et al.; Carstens and Schrodt). One alternative gives recognition to neurofibromatosis or plexiform neurofibroma as a benign precursor and distinguishes lesions in the latter category from de novo lesions which clearly have an origin within a peripheral nerve but are not associated with neurofibomatosis. In the former group, a relationship between neurofibromatosis and a malignant tumor is given recognition in the term malignant neuro-

Table 3

VARIANTS OF MALIGNANT NERVE SHEATH TUMORS

1. Malignant neuromesenchymoma
   a. fibrous and fibrohistiocytic (figs. 119, 122, 129, 130, 147–151)
   b. differentiated (rhabdomyomatous, chondroid, etc.; figs. 157–159, 162)
   c. focal glandular
2. Malignant epithelioid schwannoma (figs. 121, 131, 133, 140)
   a. transformed schwannoma
   b. de novo variant
   c. neurofibromatous (complication of neurofibromatosis)
   d. neuroid spindle cell variant (image of neurotropic melanoma; fig. 141)
3. Malignant epithelial schwannoma
   a. focal glandular differentiation in malignant schwannoma
   b. biphasic variant (epithelial and uniform spindle cell component; fig. 175)
   c. diffuse epithelial variant
4. Small cell neuroectodermal malignancy
   a. neuroepithelioma
   b. undifferentiated

fibroma. A relationship between neurofibroma and a malignant nerve sheath tumor is clearly intended. The lesions in the de novo group are classified as malignant schwannomas. From the latter term, a relationship between the malignant tumor and a benign schwannoma might be inferred, but clearly is not intended. In fact, the latter relationship is often denied or, at best, poorly documented.

Malignant tumors of nerve sheaths are divisible into two broad categories. In one, the lesions have mesenchymal qualities and commonly are associated with stigmata of neurofibromatosis: they are malignant neuromesenchymomas. In the second category, the tumor cells are epithelioid, rounded, or spindle shaped and are associated with scanty intercellular matrix. The lesions are protoplasmic and fasciculated. Some examples are associated with remnants of a benign schwannoma (malignant transformation).

Classification. Recognized variants of malignant nerve sheath tumors are shown in Table 3.

MALIGNANT NEUROMESENCHYMOMA

Definition. A malignant neuromesenchymoma is a malignant mesenchymal tumor whose cells are derived from the neural crest. It is the common expression of a malignant transformation in a plexiform neurofibroma and usually arises in the paraneurofibromatous or diffuse (neuromesenchymatous) portion. It is occasionally preceded by borderline or minimal deviation patterns. Its mesenchymal qualities are expressed in a fibrous matrix and, occasionally, in specific patterns of differentiation, including rhabdomyomatous (Woodruff et al., 1973; Karcioglu et al.), chondroid, osseous, and lipomyxomatous. In occasional patients with neurofibromatosis, malignant mesenchymomas arise in the soft tissues, but are not intimately associated with a plexiform neurofibroma (fig. 162; McKeen et al.).

Histology. The features of malignant neuromesenchymoma are listed in Table 4.

Table 4

FEATURES OF MALIGNANT NEUROMESENCHYMOMA

1. Fibrous and fibrohistiocytic variant
   a. spindle and stellate cells (figs. 130, 148)
   b. fibromyxomatous matrix (figs. 148, 149)
   c. rigid interlacing fascicles (occasional storiform patterns; figs. 148, 163)
   d. alternating light and dark fascicles (fig. 128)
   e. complex arborization of rigid fascicles
   f. focal necrosis
   g. peritheliomatous concentrations of tumor cells (figs. 153, 164)
   h. remnants of plexiform neurofibroma (fig. 154)
2. Specific patterns of differentiation admixed with the fibrous pattern
   a. rhabdomyosarcoma (fig. 159)
   b. chondrosarcoma (fig. 157)
   c. osteosarcoma (fig. 162)
   d. lipomyxosarcoma

Minimal Deviation Variant

Definition. The minimal deviation variant is a malignant neuromesenchymoma with features which deviate minimally from a diffuse neurofibroma (paraneurofibroma). In addition, it is characterized by nuclear atypism and occasional mitoses (figs. 85, 87). The tumor cells have scanty cytoplasm and plump hyperchromatic nuclei with marginated chromatin. They are loosely aggregated in a dense fibrous matrix. The rigid fascicles of a malignant neuromesenchymoma are not a regular feature of the minimal deviation variant. Nerves in the lesion are hypercellular and also show minimally deviant cellular atypism (fig. 154). Some of the cells in the altered nerves form concentric lamellae (onionskins) around axonal nerve fibers. Cellular minimal deviation changes are observed in neurofibromas adjacent to a malignant neuromesenchymoma (figs. 84, 88, 135, 138).

Prognostic Evaluation. The prognostic evaluation of a malignant neuromesenchymoma (malignant neurofibroma) involves an appreciation of cellular atypism and an estimation of the mitotic rate. In a detailed report of 46 cases, Guccion and Enzinger found 6 mitoses/10 hpf a significant parameter separating good and poor prognosis lesions. They also propose that size (7 cm. as transition zone) and location influence prognosis. The central or axial lesions have a poor prognosis when compared with acral lesions. In their series, the five-year survival rate was 15 percent. In fully evolved malignant neuromesenchymoma, the matrix, whether fibrous or myxomatous, is scanty and the tumor is uniformly cellular. In well differentiated variants, alternating fascicles are densely fibrous and mitoses are uncommon.

Patients with cancers that have been successfully treated are at risk of other malignancies in later life. Neurofibromatosis is associated with multiple malignancies. In one series, malignant schwannomas and soft tissue tumors were preceded by neuroblastoma, Wilms' tumor, and medulloblastoma (Meadows et al.)

MALIGNANT EPITHELIOID SCHWANNOMA (Including the Transformed Schwannoma)

Definition. The malignant epithelioid schwannoma is the malignant counterpart of the benign schwannoma. A similar lesion may arise de novo in a peripheral nerve or may be a rare expression of malignant transformation in a plexiform neurofibroma.

In the classification of benign nerve sheath tumors, the benign neoplasm that is composed of Schwann cells, confined by the perineurium, and anaxonal is a schwannoma. The basic, uncomplicated pattern is seen in the Antoni type A tissue. It is characterized by spindle cells which are compactly aggregated in interlacing fascicles. Intercellular fibrous matrix is usually inconspicuous and, in large part, is represented by rigid wirelike reticulum fibers.

The malignant neuromesenchymoma is usually an extraperineurial tumor derived from the paraneurofibromatous or diffuse component (neuromesenchyme) of a plexiform neurofibroma. It occasionally has its origin within the confines of an expanded perineurium. If attention is paid to the rare malignant nerve sheath tumor which arises within a preexisting benign schwannoma, a pattern (the transformed schwannoma) which significantly differs from the malignant neuromesenchymoma emerges. The

lesion, as defined by the above criteria, clearly qualifies as malignant schwannoma: it is a transformed benign schwannoma. This definition of malignant epithelioid schwannoma as a transformed benign schwannoma provides guidelines for the recognition of de novo variants. The latter, if small, generally demonstrate an origin from a peripheral nerve. They do not demonstrate a remnant of a benign schwannoma.

Histology. The transformed or malignant schwannoma and the de novo malignant epithelioid schwannoma are characterized as shown in Table 5.

Histologically, the malignant epithelioid schwannoma is composed of rigid, elongated spindle cells in interlacing fascicles. Supporting matrix is scanty and reticular. Stellate zones of necrosis with palisaded tumor cells are common. Occasionally, either uniformly or regionally, the tumor cells are spherical and have brightly acidophilic cytoplasm. Often, the round acidophilic cells form rigid files which are outlined by reticular fibers.

The round cell variant is less common and may be mistaken for an amelanotic melanoma. Round cell patterns are occasionally manifested as regional variations in the common spindle cell variants.

It is difficult to relate the pattern of a de novo malignant or transformed schwannoma to reported cases of malignant schwannoma, but the reproductions in some reports would suggest representation of this variant. It may contribute a significant number of cases to those series in which the prognosis for malignant nerve sheath tumors has been relatively good.

The division between malignant mesenchymal tumors arising in a patient with neurofibromatosis and de novo or transformed malignant epithelioid schwannomas is prognostically significant (Sordillo et al.). In the former group, most of

Table 5

HISTOLOGY OF THE TRANSFORMED OR MALIGNANT SCHWANNOMA AND THE DE NOVO MALIGNANT EPITHELIOID SCHWANNOMA

1. Plump epithelioid cells (spindle or round cells; figs. 113, 114, 121, 131–133, 140, 142, 223)
2. interlacing fascicles (rigid fascicles; figs. 115, 121, 142)
3. Inconspicuous intercellular matrix (fig. 224)
   a. reticulum fibers between cells
   b. the cellular pattern qualifies the lesion as protoplasmic (the bulk of the tumor is contributed by the expanse of cytoplasm rather than intercellular matrix)
4. Mitoses, some of which are abnormal
5. Focal collections of foamy histiocytes
6. Palisaded zones of necrosis (fig. 133)
7. Focal pleomorphism with giant cells (figs. 133, 225)

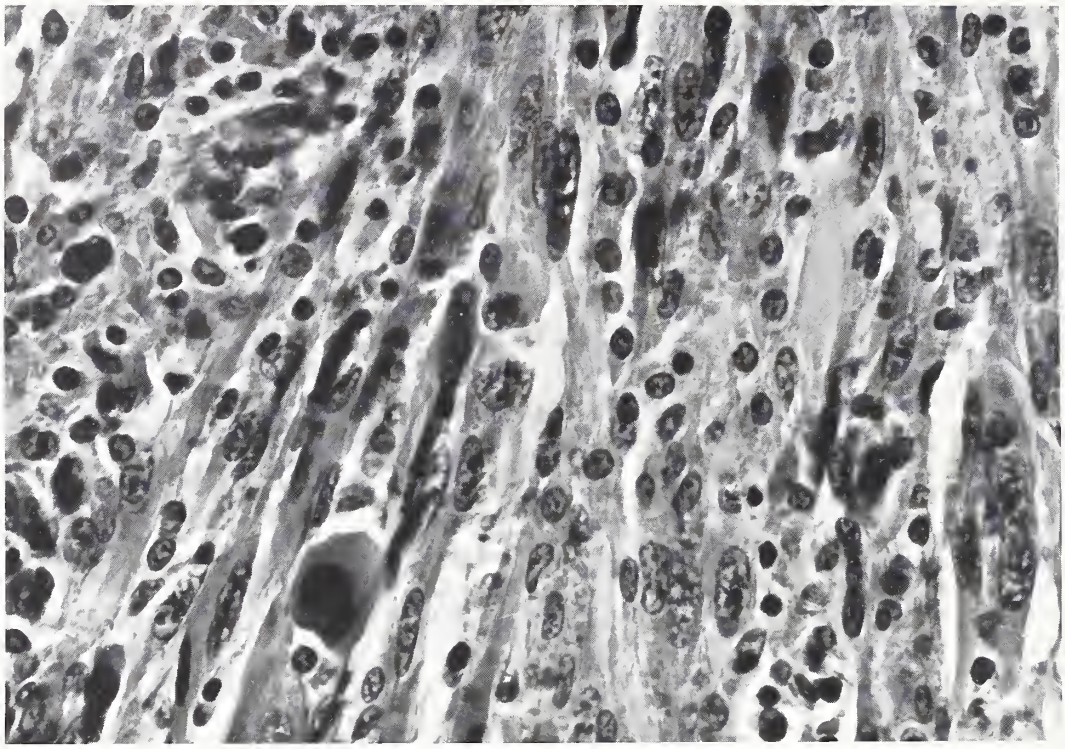

Figure 223
MALIGNANT EPITHELIOID SCHWANNOMA
The tumor cells of this malignant epithelioid schwannoma are rigid and form closely aggregated fascicles. The interstitial matrix is scant. Lymphoid cells have infiltrated the tumor. Some of the tumor cells are rounded. X400.

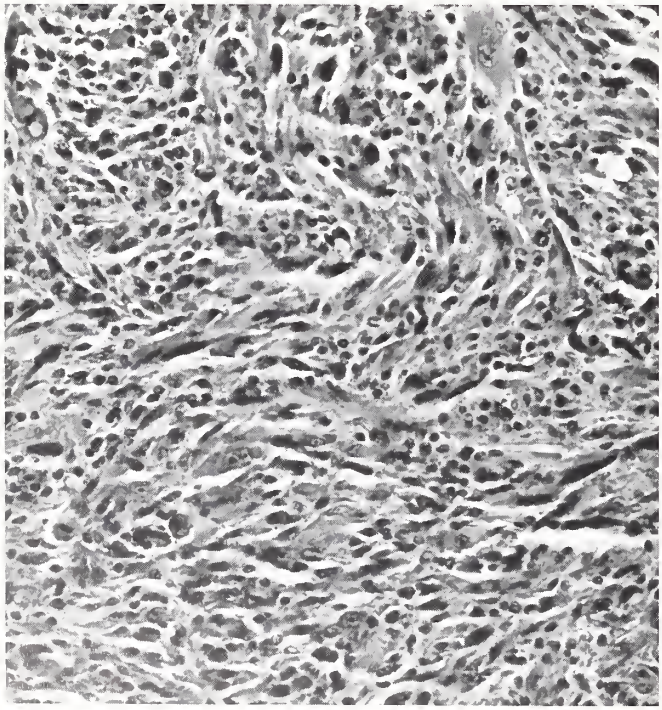

Figure 224
MALIGNANT EPITHELIOID SCHWANNOMA
In this malignant epithelioid schwannoma, rigid tumor cells form files in a relatively clear matrix. There are occasional tumor giant cells. X250.

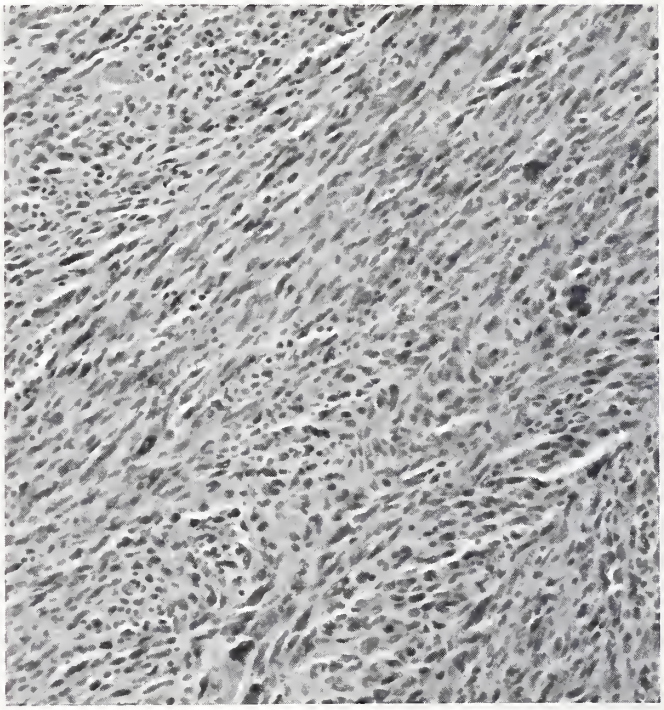

Figure 225
MALIGNANT EPITHELIOID SCHWANNOMA
This malignant epithelioid schwannoma is protoplasmic and fasciculated. There are occasional tumor giant cells. X250.

the lesions are malignant neuromesenchymomas. They are diffuse infiltrating tumors. If they are fully evolved with a significant mitotic rate, the prognosis is poor. Most of the patients will be dead within two years. In the de novo category and in transformed schwannomas, many of the tumors are circumscribed and, if arising in a benign schwannoma, are relatively confined by an expanded perineurium. They may contain melanocytes (fig. 226). If they additionally qualify as minimal deviation variants with focal storiform patterns and few mitoses (figs. 227, 228), recurrences are common within the nerve of origin. With each recurrence there may be progressive extension proximally. Metastases are unlikely at this stage. The tumor may extend into the vertebral canal and encase the spinal cord. With dedifferentiation, the tumor widely infiltrates soft tissues and metastases are likely. Some of the lesions classified as cellular schwannomas (Woodruff et al., 1981) have features of minimal deviation malignant schwannomas. The division between malignant epithelioid schwannoma and malignant neuromesenchymoma is occasionally arbitrary or impossible to clearly define.

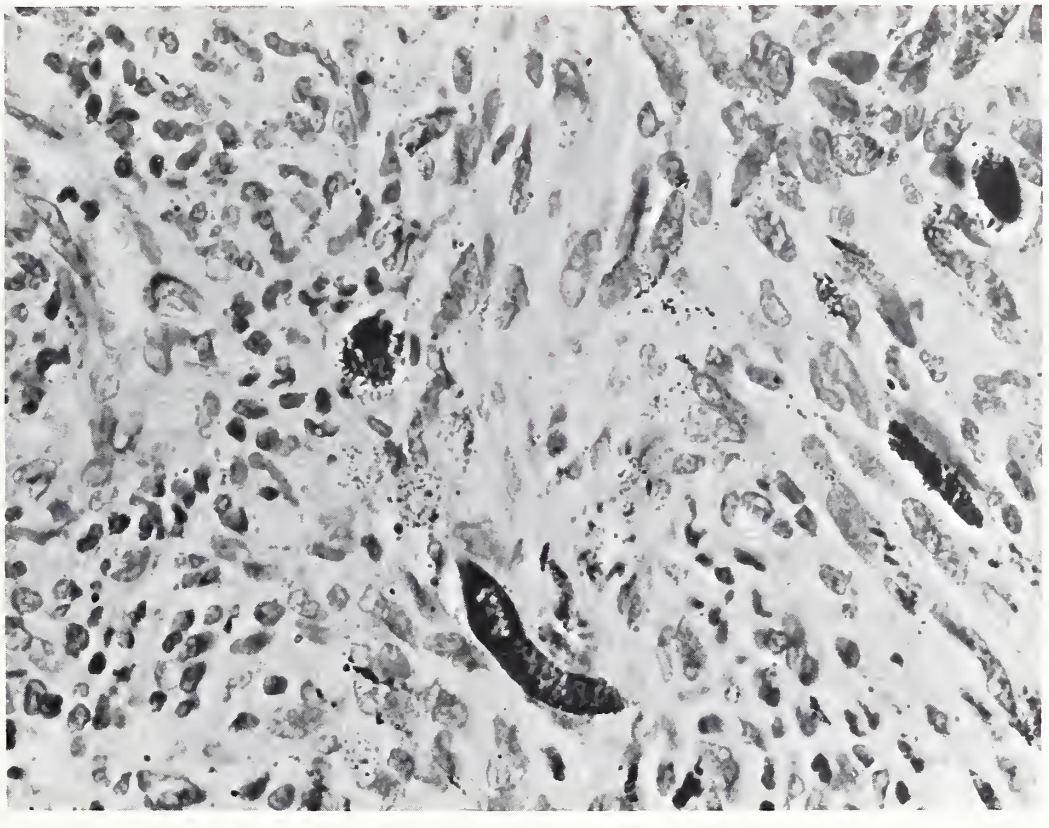

Figure 226
MALIGNANT EPITHELIOID SCHWANNOMA
Melanogenic cells are admixed with Schwann cells in this minimal deviation malignant schwannoma. Fontana-Masson stain. X400.

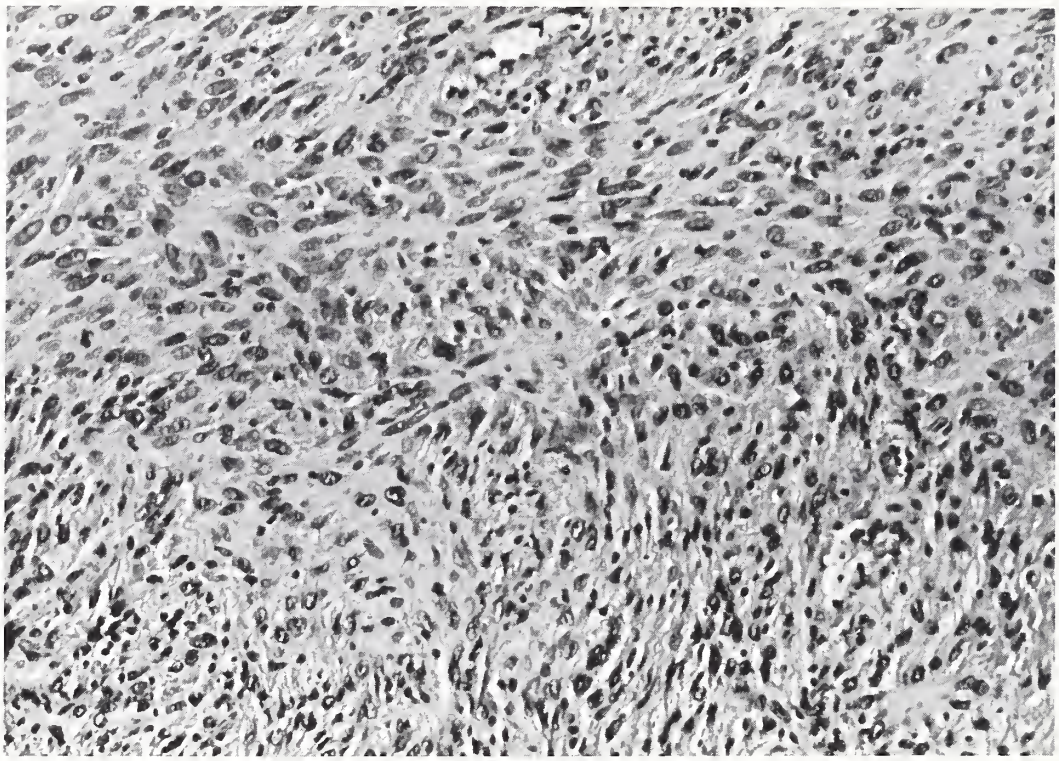

Figure 227
MALIGNANT EPITHELIOID SCHWANNOMA
Atypical Schwann cells are arranged in interlacing fascicles. The fascicles produce starburst patterns at points of intersection. This minimal deviation malignant schwannoma was a regional variation in a benign schwannoma. It was confined by the perineurium of the schwannoma. X250.

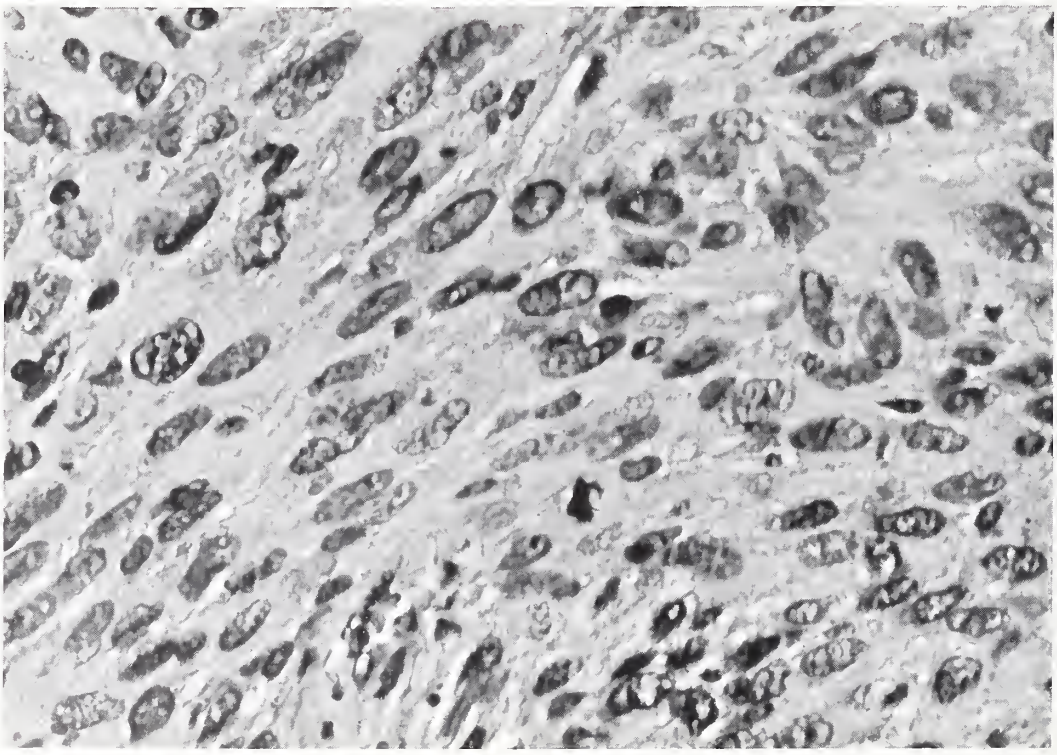

Figure 228
MALIGNANT EPITHELIOID SCHWANNOMA
The minimally deviant, cytologic quality of the tumor is illustrated in this field from a minimal deviation malignant epithelioid schwannoma. X600.

DIFFUSE EPITHELIAL MALIGNANT SCHWANNOMA

Definition. In contrast to the malignant epithelioid schwannoma, which is protoplasmic and has a diffuse matrix of reticulum fibers, the diffuse epithelial malignant schwannoma is protoplasmic and has diffuse epithelial patterns.

Histology. Nests of cells are isolated by peripheral membranes of reticulum fibers. In the nests, cells abut upon each other without intervening reticulum fibers. The pattern is monophasic (uniformly epithelial) to the exclusion of other patterns (figs. 229, 230). Tumor cells are light and dark (fig. 231). The dark cells have unipolar argyrophilic cytoplasmic extensions (fig. 232). Similar argyrophilic cells are found in both glandular and diffuse epithelial malignant schwannomas. They correspond to the dark cells seen on routine hematoxylin-eosin sections in diffuse epithelial malignant schwannoma.

An epithelial pattern may be focal and glandular in either a malignant epithelioid schwannoma or a malignant neuromesenchymoma (glandular malignant schwannoma; figs. 233, 234). In one of our cases, a carcinoma had its origin in a plexiform neurofibroma and infiltrated the neurofibroma, the overlying skin, and subcutaneous fat. It qualifies as a glandular neurocarcinoma (figs. 235, 236).

Prognosis. In our one example of a malignant epithelial schwannoma (two cases were included in the series of Guccion and Enzinger, but were not discussed separately), the clinical course was characterized by multiple local recurrences in an extremity for seven years before the appearance of distant metastases. The patient has displayed a remarkable response to chemotherapy.

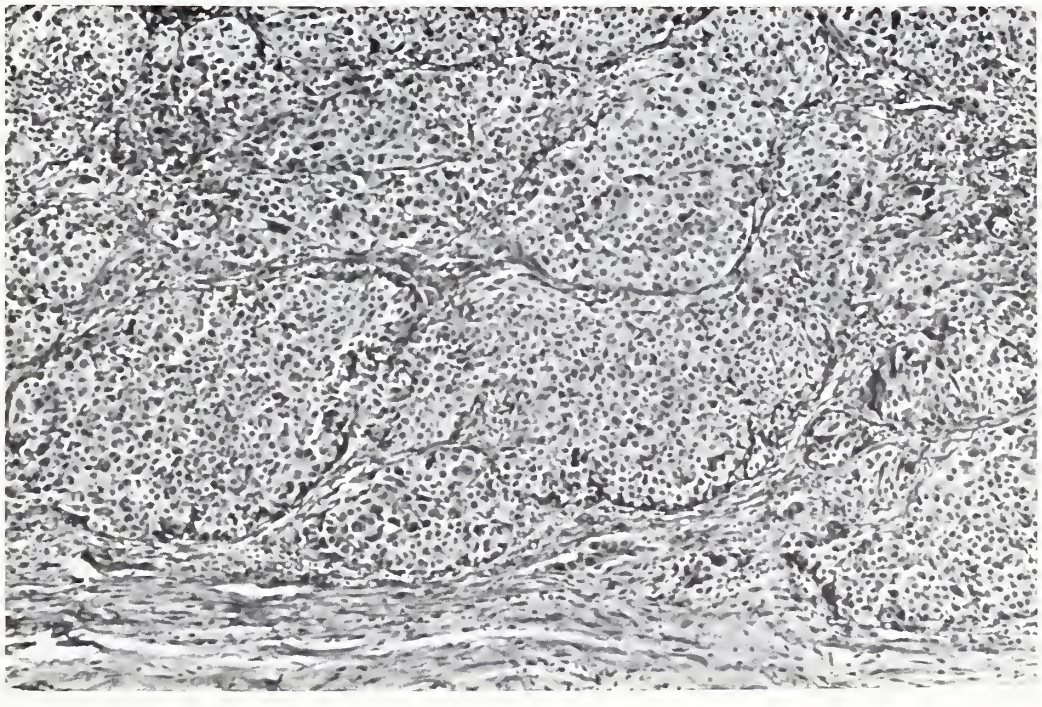

Figure 229
DIFFUSE EPITHELIAL MALIGNANT SCHWANNOMA
Plump epithelioid cells form nests and fascicles in a cellular fibrous matrix in this malignant epithelial schwannoma. X100.

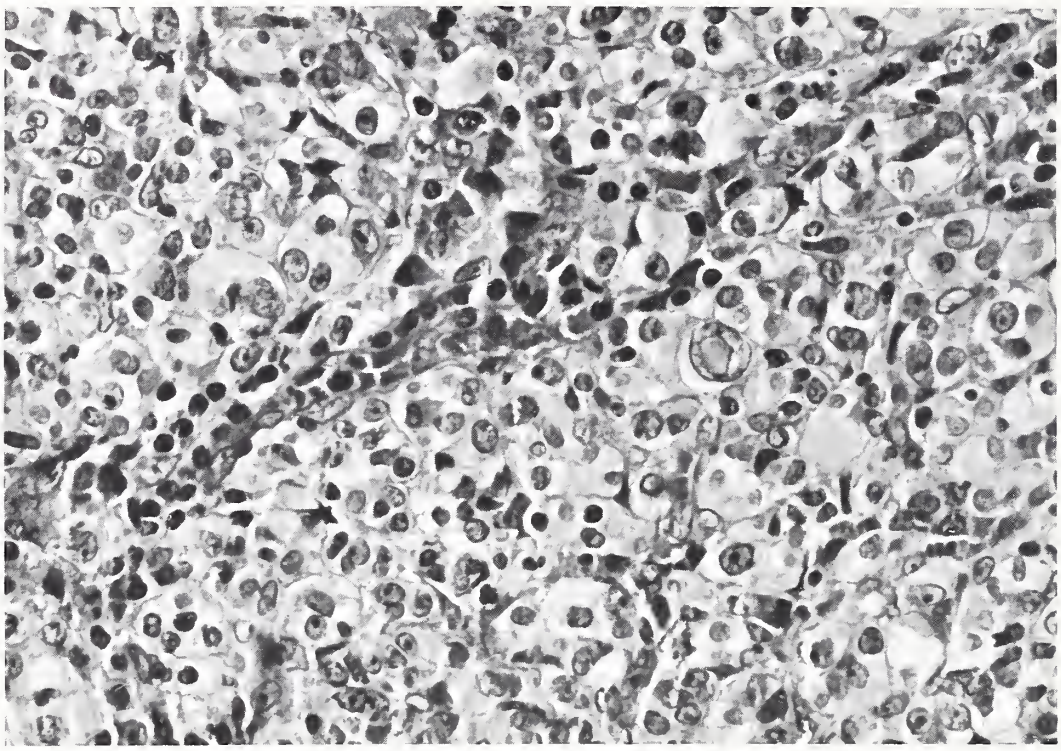

Figure 230
DIFFUSE EPITHELIAL MALIGNANT SCHWANNOMA
The tumor cells of this malignant epithelial schwannoma are rounded and have pale, glassy cytoplasm. The cytoplasm protrudes into the nuclei of some of the tumor cells. Light and dark cells are represented. X250.

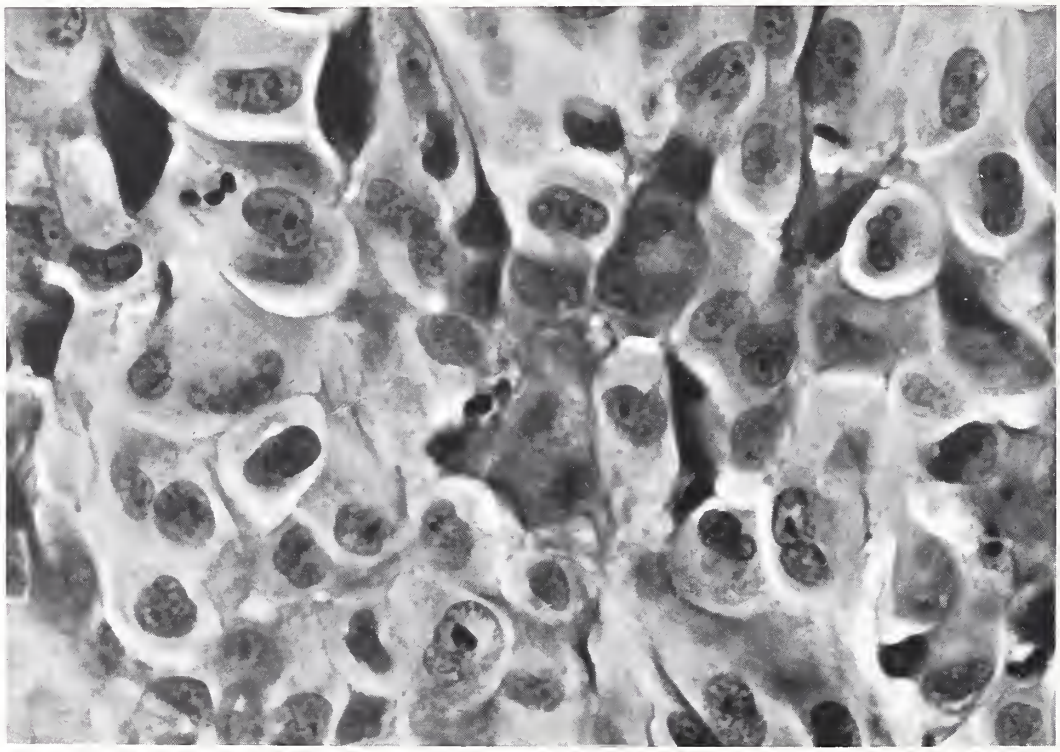

Figure 231
DIFFUSE EPITHELIAL MALIGNANT SCHWANNOMA
The tumor cells have homogeneous or glassy cytoplasm. They have stippled chromatin and prominent nucleoli. The dark cells have easily identified rigid cytoplasmic processes. X600.

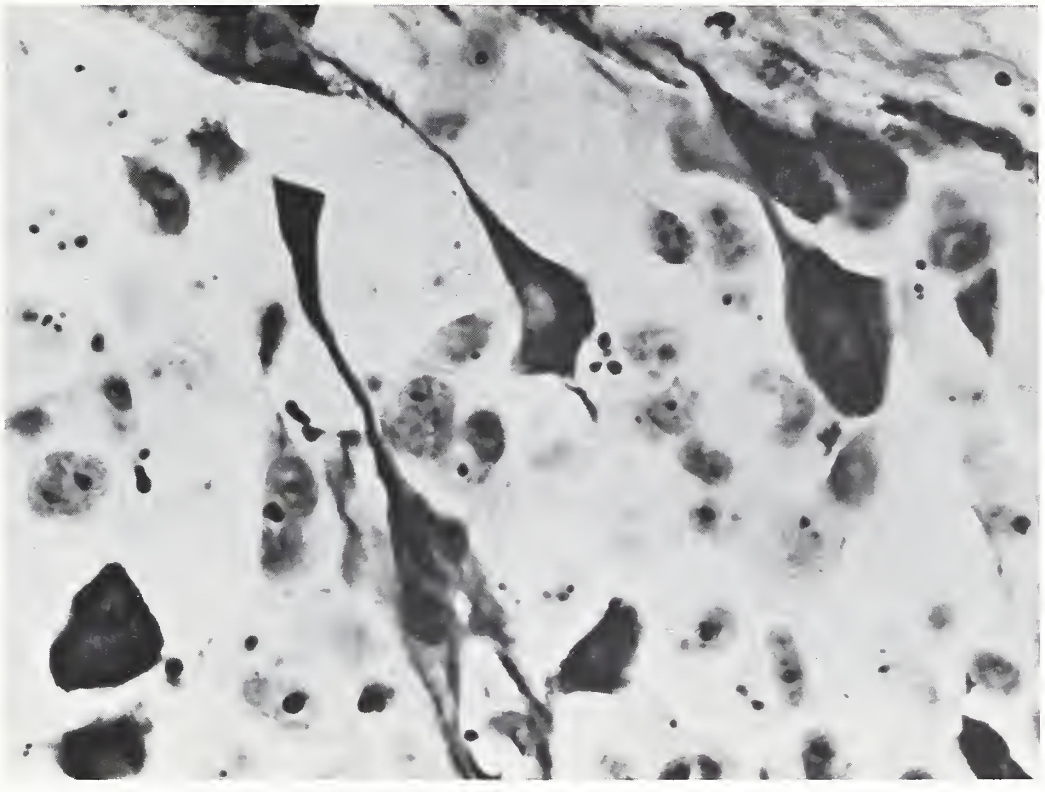

Figure 232
DIFFUSE EPITHELIAL MALIGNANT SCHWANNOMA
The cytoplasmic processes of the dark cells in this malignant epithelial schwannoma are argyrophilic. Bodian method. X600.

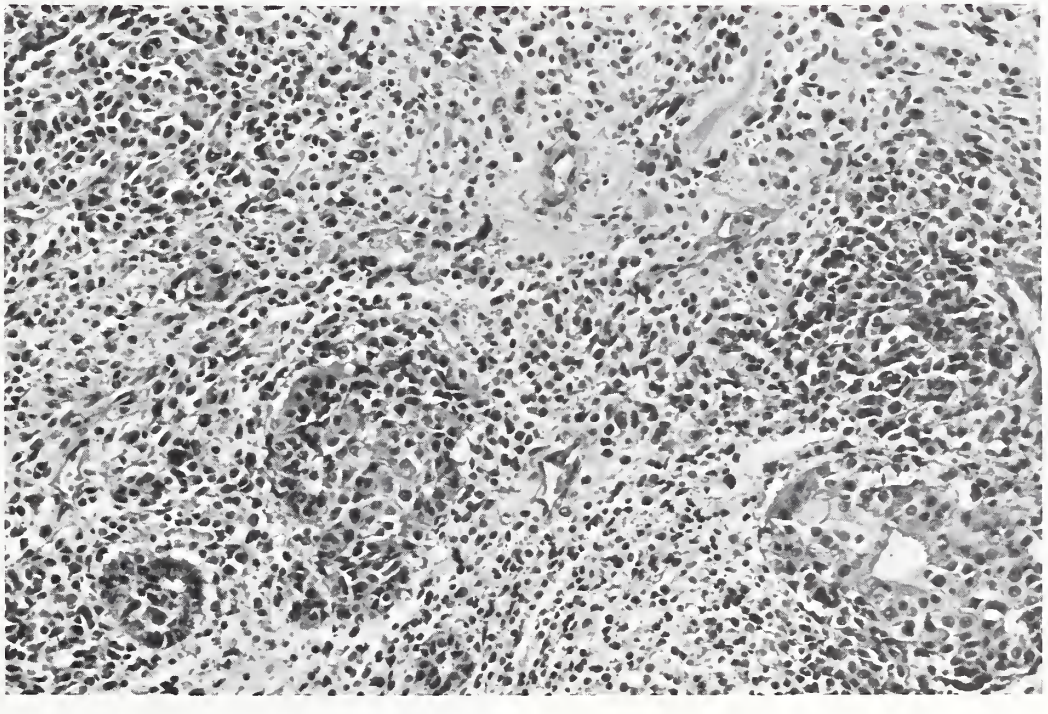

Figure 233
MALIGNANT EPITHELIOID SCHWANNOMA
In this malignant epithelioid schwannoma, some of the tumor cells are arranged in epithelial and glandular patterns. X100.

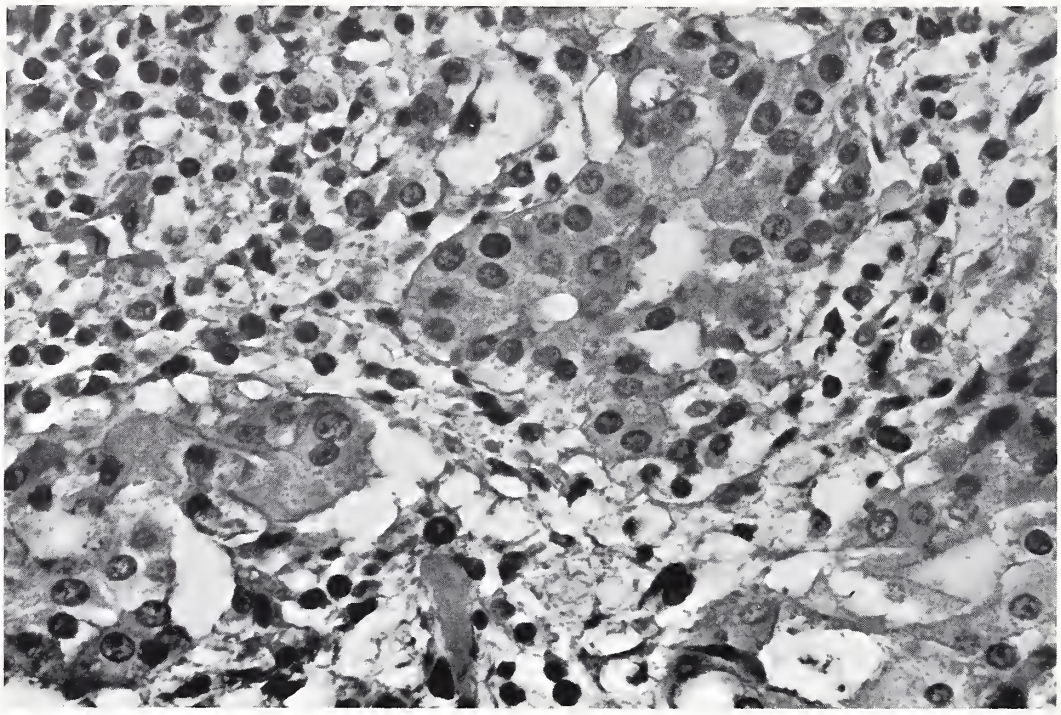

Figure 234
GLANDULAR MALIGNANT SCHWANNOMA
The epithelial component of this glandular malignant schwannoma is illustrated. The vacuoles within the glandular component contain acid mucopolysaccharides. X250.

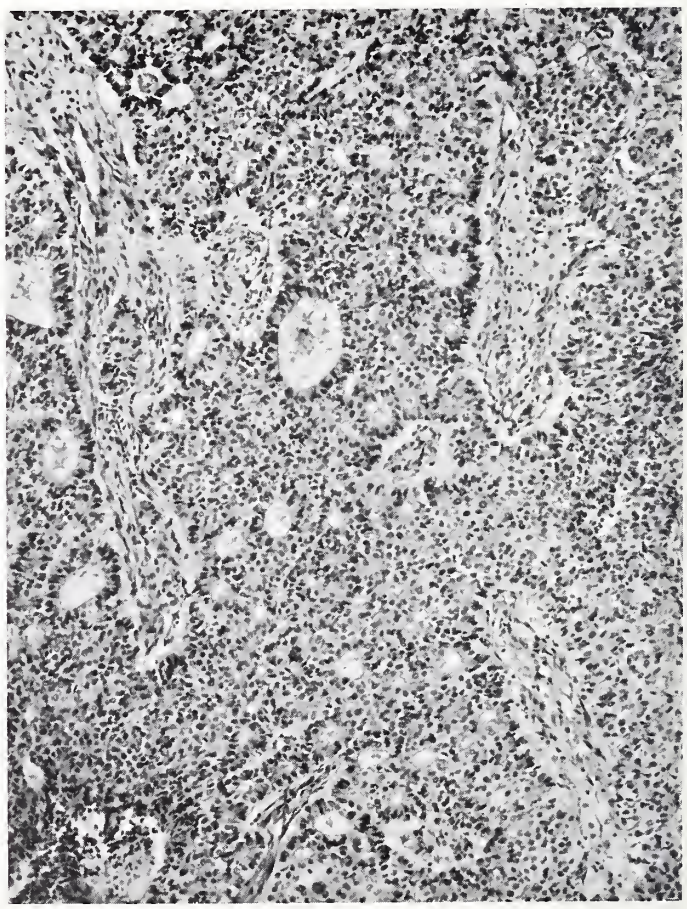

Figure 235
PERIPHERAL GLANDULAR NEUROCARCINOMA
This peripheral glandular neurocarcinoma had its origin in a plexiform neurofibroma. It infiltrated the tumor of origin, the overlying skin, and subcutaneous fat. It is composed of columnar cells in glandular patterns. Many of the cells have clear cytoplasm. Darker compressed cells are irregularly interspersed. In solid portions, the tumor cells are plump and rounded. There are irregular spicular deposits of hyaline material. Some of the tumor cells in the solid areas and, focally, in the glandular areas have a moderate amount of acidophilic cytoplasm. The glandular spaces contain mucicarminophilic material. X97.

NEUROEPITHELIOMA OF PERIPHERAL NERVES

Definition. Neuroepithelioma of peripheral nerves is a malignant neoplasm of peripheral nerves in which small cells are arranged in rosettes and pseudorosettes. The tumor is rare (Nesbitt and Vidone). Some of the reported cases are peripheral neuroblastomas with dense core vesicles (Bolen and Thorning). Some are true glandular tumors with mucicarminophilic cells. In the latter category, the glandular changes have been focal in a "malignant schwannoma," usually as a transformation in a plexiform neurofibroma (Woodruff). We have seen one example which was uniformly glandular (peripheral neurocarcinoma) and involved a plexiform neurofibroma (figs. 235, 236).

MALIGNANT UNDIFFERENTIATED SMALL CELL TUMOR OF PERIPHERAL NERVES

A small cell undifferentiated malignant tumor of peripheral nerves (fig. 237) may be confused with malignant lymphoma. It qualifies as an undifferentiated variant of the malignant neuroepithelioma or a peripheral neuroblastoma.

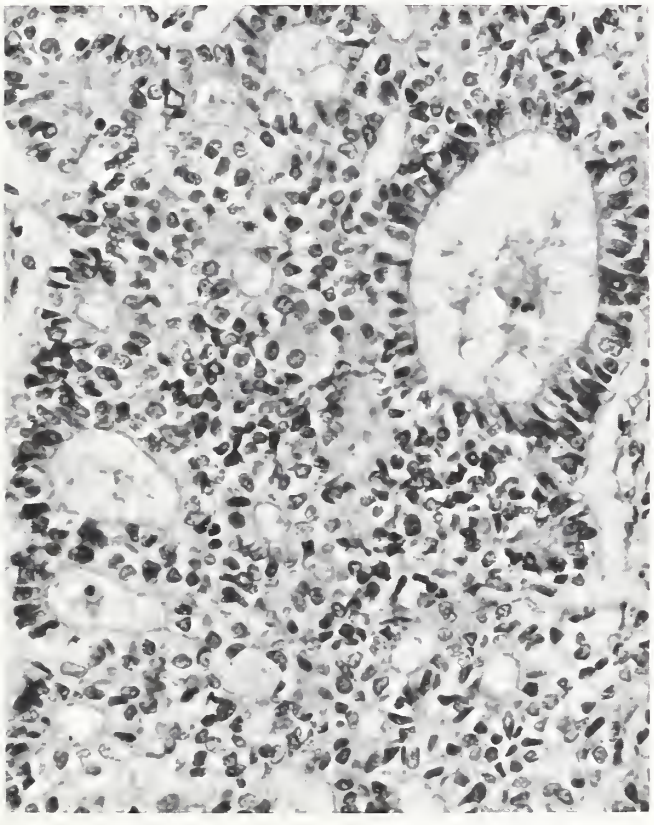

Figure 236
PERIPHERAL GLANDULAR NEUROCARCINOMA
Pseudostratified light and dark cells form glandular patterns in this neurocarcinoma. Ultrastructurally, uniform microvilli project from the luminal surfaces of the tumor cells. X260.

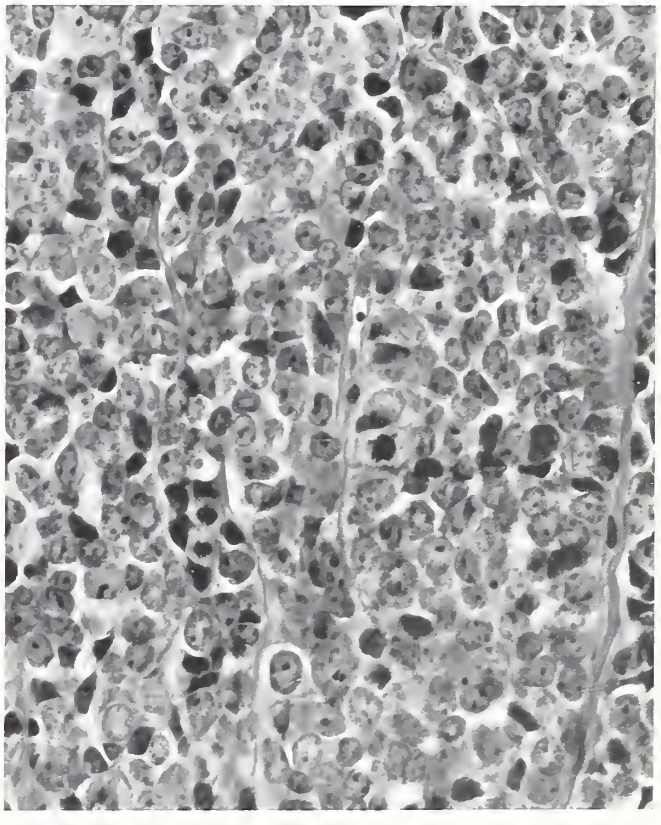

Figure 237
MALIGNANT UNDIFFERENTIATED SMALL CELL TUMOR
This small cell undifferentiated malignant neoplasm of peripheral nerves has displaced the normal components. The tumor cells have scanty cytoplasm, delicate chromatin, and one or more prominent nucleoli. X400.

References

Bolen, J. W. and Thorning, D. Peripheral neuroepithelioma. Cancer 46:2456-2462, 1980.

Carstens, P. H. B. and Schrodt, G. R. Malignant transformation of a benign encapsulated neurilemoma. Am. J. Clin. Pathol. 51:144-149, 1969.

D'Agostino, A. N., Soule, E. H., and Miller, R. H. Primary malignant neoplasms of nerves (malignant neurilemomas) in patients without manifestations of multiple neurofibromatosis (von Recklinghausen's disease). Cancer 16:1003-1014, 1963a.

_____, Soule, E. H., and Miller, R. H. Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease). Cancer 16:1015-1027, 1963b.

DasGupta, T. K. and Brasfield, R. D. Solitary malignant schwannoma. Ann. Surg. 171:419-428, 1970.

Ghosh, B. C., Ghosh, L., Huvos, A. G., and Fortner, J. C. Malignant schwannoma. Cancer 31:184-190, 1973.

Guccion, J. G. and Enzinger, F. M. Malignant schwannoma associated with von Recklinghausen's neurofibromatosis. Virchows Arch. [Anat. Pathol.] 383:43-57, 1979.

Karcioglu, Z., Someren, A., and Mathes, S. J. Ectomesenchymoma: A malignant tumor of migratory neural crest (ectomesenchyme) remnants showing ganglionic, schwannian, melanocytic and rhabdomyoblastic differentiation. Cancer 39:2486-2496, 1977.

Meadows, A. T., D'Angio, G. J., Miké, V., Banfi, A., Harris, C., Jenkin, R. D. T., and Schwartz, A. Patterns of second malignant neoplasms in children. Cancer 40:1903-1911, 1977.

McKeen, E. A., Bodurtha, J., Meadows, A. T., Douglass, E. C., and Mulvihill, J. J. Rhabdomyosarcoma complicating multiple neurofibromatosis. J. Pediatr. 93:992-993, 1978.

Nesbitt, K. A. and Vidone, R. A. Primitive neuroectodermal tumor (neuroblastoma) arising in sciatic nerve of a child. Cancer 37:1562-1570, 1976.

Russell, D. S. and Rubinstein, L. J. Pathology of Tumours of the Nervous System, pp. 48-55, 372-398. 4th Ed. Baltimore: Williams and Wilkins Co., 1977.

Sordillo, P. P., Helson, L., Hajdu, S. I., Magill, G. B., Kosloff, C., Golbey, R. R., and Beattie, E. J. Malignant schwannoma — Clinical characteristics, survival and response to therapy. Cancer 47:2503-2509, 1981.

Taxy, J. B., Battifora, H., Trujillo, Y., and Dorfman, H. D. Electron microscopy in the diagnosis of malignant schwannoma. Cancer 48:1381-1391, 1981.

Woodruff, J. M. Peripheral nerve tumors showing glandular differentiation (glandular schwannomas). Cancer 37:2399-2413, 1976.

_____, Chernik, N. L., Smith, M. C., Millett, W. B., and Foote, F. W., Jr. Peripheral nerve tumors with rhabdomyosarcomatous differentiation (malignant "triton" tumors). Cancer 32:426-439, 1973.

_____, Godwin, T. A., Erlandson, R. A., Susin, M., and Martini, N. Cellular schwannoma. Am. J. Surg. Pathol. 5:733-744, 1981.

NEUROTROPIC MELANOMA

Introduction. The perineurial cell is a functional variant of the Schwann cell. Observations as to the embryologic heritage of the Schwann cell pertain equally to the perineurial cell.

The neural crest and dysplasias. The Schwann cell and the melanocyte are close embryologic relatives (Weston). Their common heritage is expressed in paraneurofibromas in which tactoid bodies and melanocytes are often associated. The tactoid body is a specialized collection of sheath or perineurial cells. A melanocyte is generally a resident of epithelium rather than mesenchyme. In mesenchyme, it is usually associated with a dysplasia. The tactoid body and the mesenchymal melanocyte are markers for neuromesenchyme (Reed; Masson).

The natural history of the acquired melanocytic nevus is a migration from epithelium to mesenchyme, a progressive loss of melanogenic functions and the acquisition of perineurial qualities (formation of tactoid bodies during the process of neurotization) (Pease and Pallie). The process is a distorted recapitulation of the formation of the papillary dermis and its specialized structures (tactoid bodies). It is also a recapitulation of an embryonic migration of neurocristic effector cells to the developing dermal mesenchyme. The melanocyte is mutable with the potential to function as, or phenotypically transform to, a mesenchymal cell or perineurial (Schwann) cell. The available evidence implicates a role for neurocristic effector cells in the formation of the dermis.

The mesenchymal properties of melanocytes are also expressed in the congenital nevus. Files of tumor cells between collagen bundles are markers for the defective incorporation of neurocristic effector cells in the developing reticular dermis.

THE SPINDLE MELANOCYTE, DESMOPLASIA, AND NEUROTROPISM

Desmoplastic melanomas are a peculiar expression of the mesenchymal properties of melanocytes (Conley et al.; figs. 238, 239). In lesions with lentiginous radial

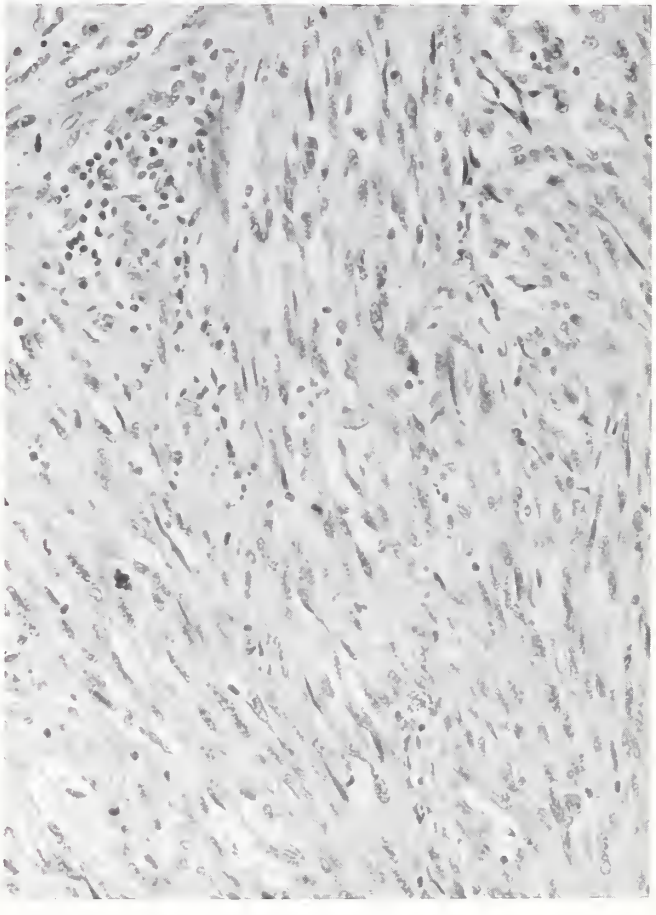

Figure 238
DESMOPLASTIC MELANOMA
In this desmoplastic lentiginous melanoma, the tumor cells are spindle shaped and fibrogenic. There are occasional mitotic figures. Nuclei are relatively uniform. Nuclear atypism in this variant is often deceptive. X250.

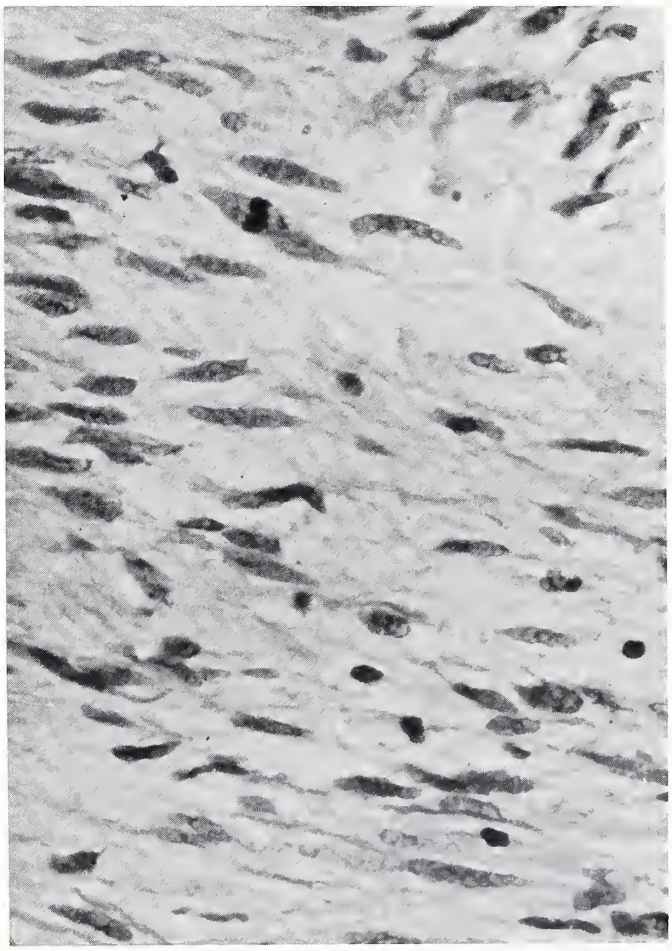

Figure 239
DESMOPLASTIC MELANOMA
The desmoplastic tumor cells are widely spaced in a fibrous matrix in this melanoma. X250.

growth, vertical growth is usually expressed by spindle melanocytes. Desmoplastic melanomas are usually associated with lentiginous radial growth. The spindle melanocyte is often desmoplastic and commonly manifests a preference for residence in the reticular rather than the papillary dermis. In addition, the spindle melanocyte has a predilection for peripheral nerves (neurotropism). In some melanomas, neurotropism finds a peculiar expression in which the involved nerves become the loci for the growth of the tumor and for recurrences (Reed and Leonard). These peculiar neurocristic tumors are **neurotropic melanomas.**

PRECURSORS OF NEUROTROPIC MELANOMAS

The precursors for neurotropic melanomas are usually lentiginous melanomas (Reed and Leonard). Most commonly, the precursor is lentigo maligna melanoma, often in its desmoplastic phase. Rarely, the precursor qualifies as a minimal deviation melanoma in which cytologic and histologic features deviate minimally from a benign melanocytic nevus. Some neurotropic melanomas, particularly on the lip, arise de novo from epidermal melanocytes without a recognizable precursor (de novo variant; fig. 240).

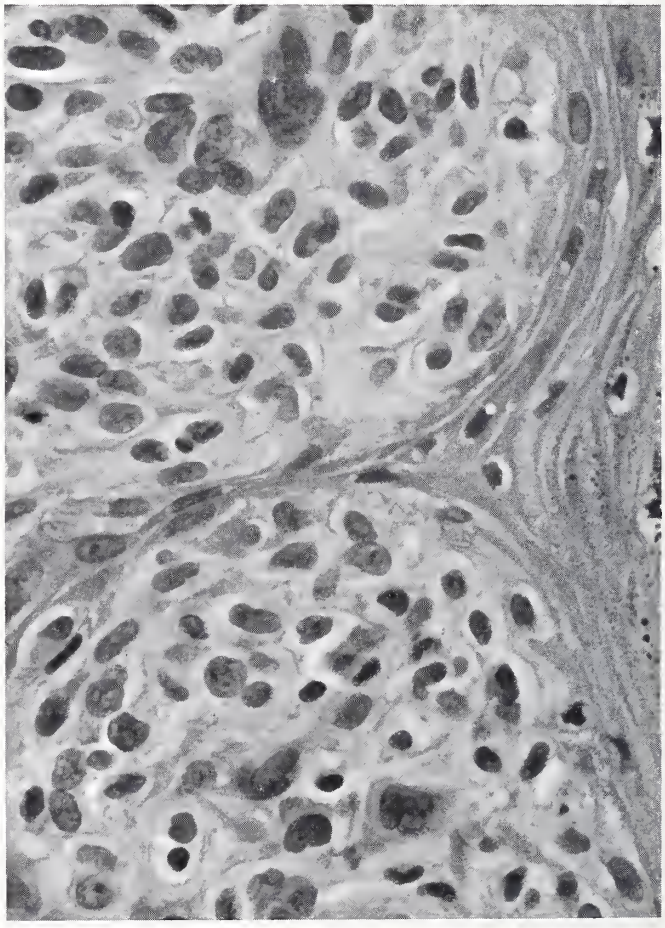

Figure 240
NEUROTROPIC MELANOMA
Fascicles of atypical spindle cells extend from the dermal-epidermal interface into the dermis in this de novo neurotropic melanoma. X400.

Histology. The neurotropic phase is characterized by the invasion of peripheral nerves and the intermingling of tumor cells and Schwann cells in the formation of primary units. Tortuous rigid fascicles of spindle cells extend from the infiltrated nerve into the dermis (figs. 241, 242). They disperse in the dermis in the pattern of a traumatic neuroma. The pattern may be subtle and merge with desmoplastic melanoma (fig. 243). The fascicles usually have well defined interfaces with the invaded mesenchyme and often display a peripheral concentric layer which resembles a perineurium (fig. 242). The spindle cells have pale cytoplasm, distinct cell membranes, and plump irregular hyperchromatic nuclei (figs. 244, 245). The cells are supported by rigid, wirelike reticular fibers. Some of the fascicles of malignant cells contain argyrophilic fibers with the tinctorial qualities of axons (fig. 246). Either the neoplastic cells have argyrophilic processes, or some of the fascicles of tumor cells are innervated (axonal). The tumor cells acquire the characteristics of Schwann cells (Warner et al.).

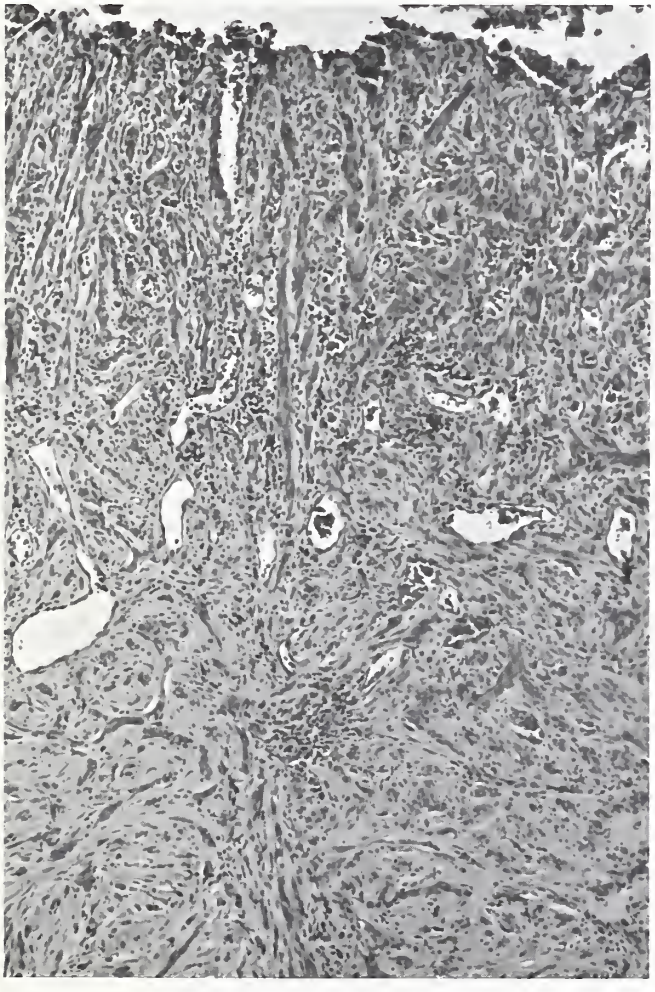

Figure 241
NEUROTROPIC MELANOMA
In this recurrent neurotropic melanoma, the fascicles are widely spaced in the reticular dermis. The epidermis is ulcerated. X40.

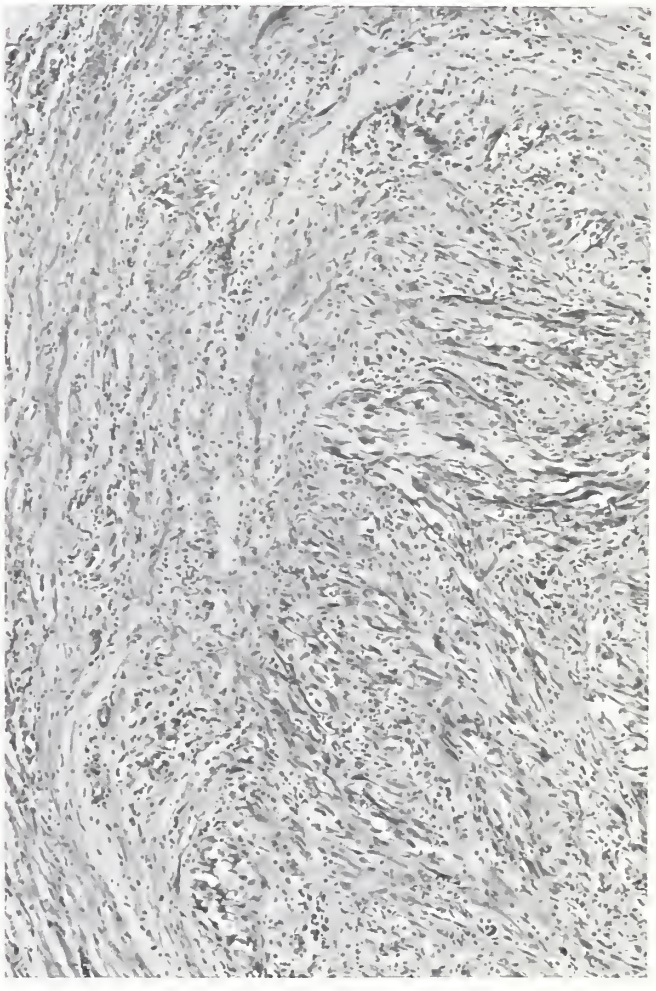

Figure 242
NEUROTROPIC MELANOMA
This neurotropic pattern is often best displayed at the deep margin of the dermis and in the subcutis. The fascicles are coarse and widely spaced in an inflamed fibrous matrix. They are arranged in neuroid patterns. X100.

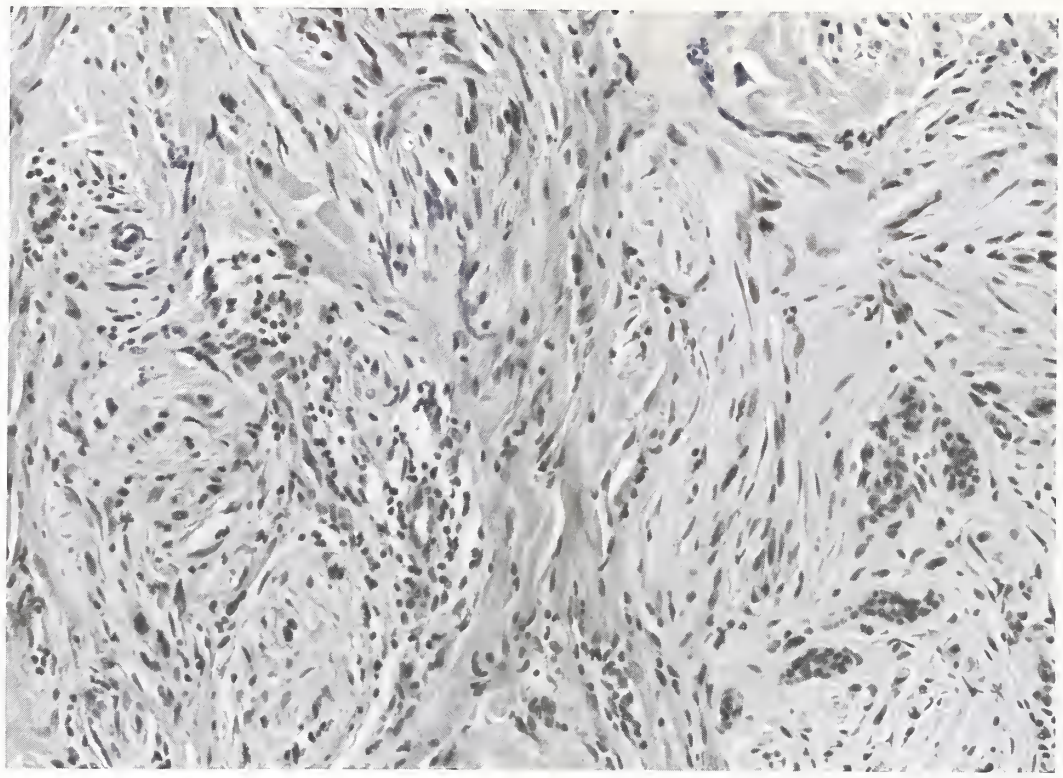

Figure 243
NEUROTROPIC MELANOMA
The neurotropic pattern blends with the pattern of desmoplastic melanoma. Cytologic atypism is often minimal in this variant of melanoma. X250.

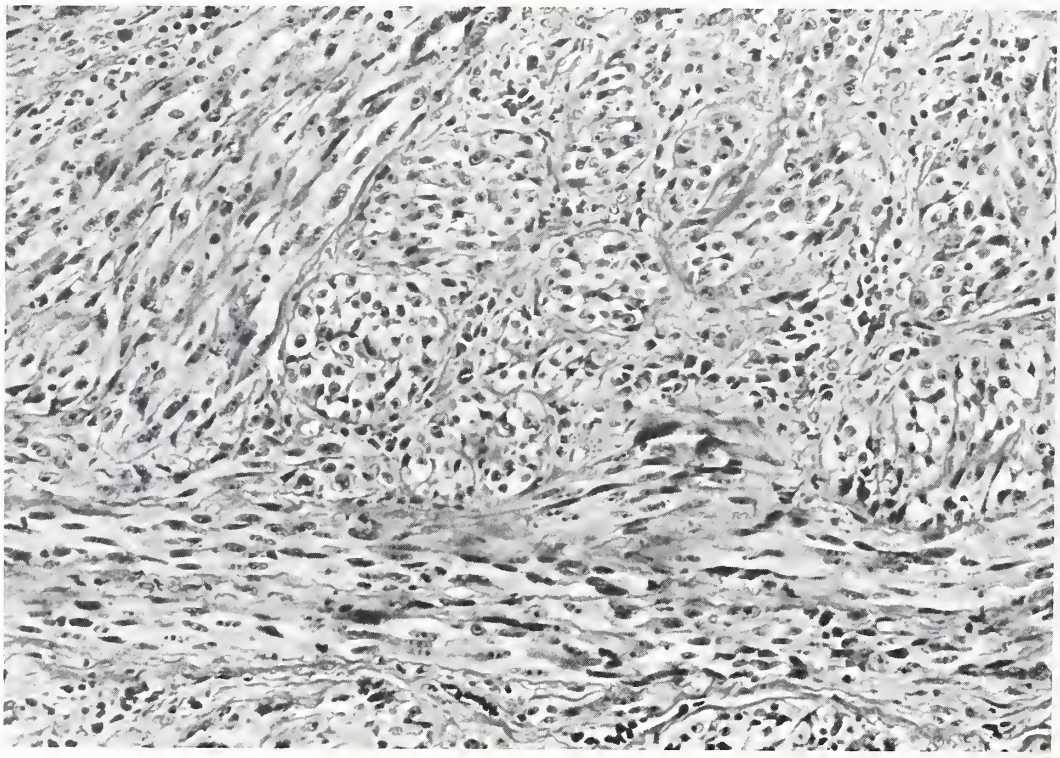

Figure 244
NEUROTROPIC MELANOMA
In a late recurrence with dedifferentiation, the tumor cells show progressive dysplasia. The fascicles of cells are coarse and compactly aggregated. X250.

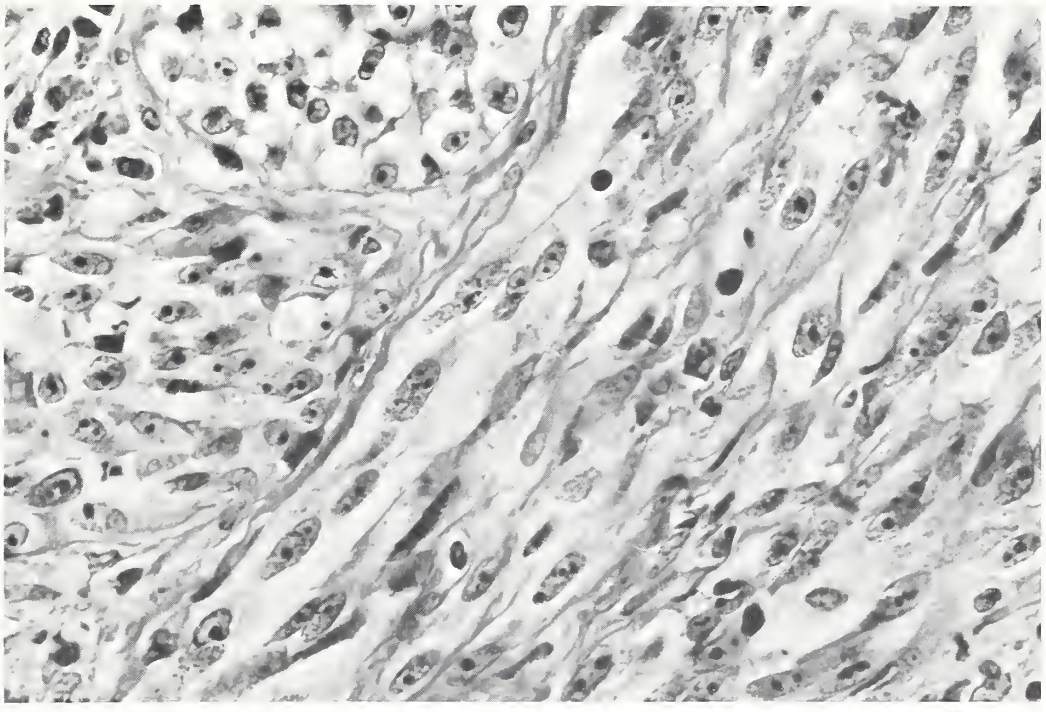

Figure 245
NEUROTROPIC MELANOMA
The cytologic features of tumor cells in a dedifferentiated neurotropic melanoma are illustrated. X400.

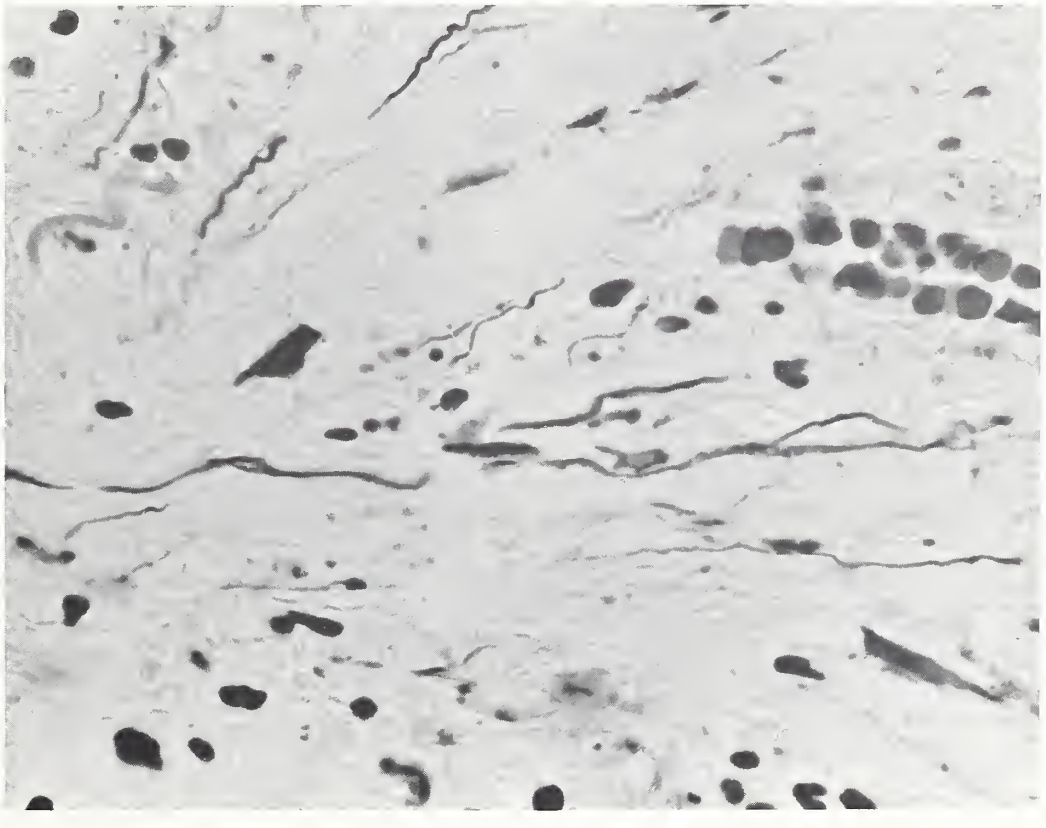

Figure 246
NEUROTROPIC MELANOMA
In some examples of neurotropic melanoma, rigid argyrophilic fibers that have axonal qualities are present in the fascicles of tumor cells. Bodian method. X60.

The involved nerves become the growth centers for the tumor. In recurrences, markers for the precursors are not apparent. The tumor cells, with rare exceptions, are amelanotic. The de novo variant may demonstrate epidermotropism in recurrences, even after intervals of several years between recurrences. The fascicles of tumor cells reseed the organizing scar after incomplete excisions. They recapitulate the neuromatous pattern. In early phases of the process, the tumor cells often show deceptively bland cytologic characteristics. In late phases, usually after several recurrences, the tumor cells show progressive anaplasia, a feature often associated with dissemination of the disease by lymphatics and the blood stream. The tumor also progressively infiltrates along the peripheral nerves. It may extend directly into the cranial cavity.

The neurotropic properties which are exhibited by some melanomas reinforce the concept of the mutability of Schwann cells and melanocytes. In the neurotropic melanoma, tumor cells generally lose their melanogenic properties and acquire Schwann cell (neurosustentacular) characteristics. They may even function as sheath cells for axons.

A comparable neuroid tumor is occasionally primary in a peripheral nerve in the deep soft tissues. It qualifies as a malignant epithelioid schwannoma, but is histologically indistinguishable from the neurotropic melanoma. It may contain argyrophilic fibers which resemble axon cylinders. Similar argyrophilic fibers may be demonstrated in desmoplastic melanomas. They may express peculiar argyrophilic properties of the cytoplasmic processes of tumor cells or may be hyperplastic axons.

References

Conley, J., Lattes, R., and Orr, W. Desmoplastic malignant melanoma (a rare variant of spindle cell melanoma). Cancer 28:914-936, 1971.

Mark, G. J., Mihm, M. C., Liteplo, M. G., Reed, R. J., and Clark, W. H. Congenital melanocytic nevi of the small and garment type. Hum. Pathol. 4:395-418, 1973.

Masson, P. Human Tumors: Histology, Diagnosis, and Technique, pp. 1055, 1103, 1079-1086. 2d Ed. Translated by Kobernick, S. D. Detroit: Wayne State Univ. Press, 1970.

Pease, D. C. and Pallie, W. Electron microscopy of digital tactile corpuscles and small cutaneous nerves. J. Ultrastruct. Res. 2:352-365, 1959.

Reed, R. J. Cutaneous manifestations of neural crest disorders (neurocristopathies). Int. J. Dermatol. 16:807-826, 1977.

——— and Leonard, D. D. Neurotropic melanoma; a variant of desmoplastic melanoma. Am. J. Surg. Pathol. 3:301-311, 1979.

Warner, T. F., Hafez, G. R., Finch, R. E., and Brandenberg, J. H. Schwann cell features in neurotropic melanoma. J. Cutan. Pathol. 8:177-187, 1981.

Weston, J. A. The Regulation of Normal and Abnormal Neural Crest Cell Development, pp. 77-95. In: Advances in Neurology, Vol. 29, Neurofibromatosis. Riccardi, V. M. and Mulvihill, J. J. (Eds.). New York: Raven Press, 1981.

CLEAR CELL SARCOMA

Definition. The clear cell sarcoma is a soft tissue sarcoma in which some of the spindle cells have clear cytoplasm and occasionally are melanogenic (Enzinger; Boudreux and Waisman).

This distinctive tumor involves fascia and aponeuroses and may arise in the subcutaneous fat. In the melanogenic foci, the pattern overlaps with foci seen in some malignant blue nevi. Histogenetically, the neural crest has been implicated as the embryologic precursor. In the Fascicle (pp. 123–125), the malignant melanocytic schwannoma represents a variant of clear cell sarcoma.

It has recently been proposed that clear cell sarcomas are histogenetically heterogeneous and include a melanocytic variant and a synovial variant (Tsuneyoshi et al.). Criteria for distinguishing the two have been proposed, but, in practice, the two patterns are occasionally combined in a single tumor.

Differential Diagnosis. Pigmented neuroectodermal tumors (pigmented schwannomas) have been reported as intradural extramedullary tumors and as lesions of the peripheral nerve ganglia (Mennemeyer et al.). They are composed of pigmented spindle cells. In some examples, the cells are compactly aggregated in fascicles. In other examples, the cells are widely spaced in a clear matrix and have complex cytoplasmic processes. In the latter variant, calcospherites are a common feature. Ultrastructurally, the tumor cells have Schwann cell qualities. These tumors usually are classified as melanotic schwannomas. The clinical course is variable, but some examples have recurred locally or metastasized. In this category, it may be difficult to make a distinction between melanotic schwannoma and melanotic clear cell sarcoma (Parker et al.).

References

Boudreux, D. and Waisman, J. Clear cell sarcoma with melanogenesis. Cancer 41:1387-1394, 1978.

Enzinger, F. M. Clear cell sarcoma of tendons and aponeurosis. Cancer 18:1163-1174, 1965.

Mennemeyer, R. P., Hallman, K. O., Hammar, S. P., Raisis, J. E., Tytus, J.,S., and Bockus, D. Melanotic schwannoma: Clinical and ultrastructural studies of three cases with evidence of intracellular melanin synthesis. Am. J. Surg. Pathol. 3:3-10, 1979.

Parker, J. B., Marcus, P. B., and Martin, J. H. Spinal melanotic clear-cell sarcoma. Cancer 46:718-724, 1980.

Tsuneyoshi, M., Enjoji, M., and Kubo, T. Clear cell sarcoma of tendons and aponeuroses. Cancer 42:243-252, 1978.

MISCELLANEOUS

Interstitial pulmonary fibrosis and neurofibromatosis. An association between neurofibromatosis and some examples of diffuse interstitial fibrosis of the lungs has been documented (Patchefsky et al.; Webb and Goodman). In some of these cases, the upper lobes have also contained bullae. Histologically, the lungs show mild interstitial fibrosis and desquamation of alveolar cells. Ultrastructurally, the desquamated cells have the qualities of macrophages, but are attached to neighbors by tight junctions. The process apparently does not have an immunologic basis. It usually affects adults with neurofibromatosis.

Scoliosis and neurofibromatosis. Scoliosis is a complication of neurofibromatosis. In a review of over 3000 cases, the incidence of scoliosis was 3 percent (Rezaian). The cases fall into two categories: (1) a mild form in which the disease is relatively stable, and (2) a severe form in which progressive deterioration of the spine occurs in adults.

Peripheral and central variants of neurofibromatosis. The division between peripheral and central variants is fairly consistent within a given family (Kanter et al.). The distinctions apparently are genetic and find expression in the biochemistry of nerve growth factor (NGF). In the central variant, high levels of antigenically active NGF are demonstrated by competitive radioimmunoassay. In the peripheral variant, high levels of functionally active NGF are demonstrated by competitive radioreceptor assay. The clinical, genetic, and biochemical characteristics of central and peripheral neurofibromatosis recently have been compared (Eldridge).

Tactoid bodies, Schwann cells, perineurial cells, and axons. Tactoid bodies are composed of laminated sheath cells. In some examples, the cells have perineurial qualities. In other examples, the peripheral cells have perineurial qualities and the more central cells have schwannian qualities (Smith and Bhawan). In some tactoid bodies, myelinated or nonmyelinated axons are ensheathed by the laminated cells. Tactoid bodies are dysplastic images of Meissner's corpuscles.

Radiotherapy and malignant tumors of nerve sheaths. Malignant tumors of nerve sheath may arise within tissue that has been subjected to x-irradiation. The interval between irradiation and the appearance of the malignancy is usually years. Some of the lesions have arisen in neurofibromas in the irradiated sites, but others apparently were spontaneous and were not associated with stigmata of neurofibromatosis (Foley et al.).

Experimentally induced tumors of peripheral nerves. Nitrosourea derivatives are potent carcinogens with a high specificity for the nervous system of experimental animals (Cravioto et al.). The tumors are composed of Schwann cells and behave as malignancies. The tumor cells lose their basal lamina during dedifferentiation. By electron microscopy, basal lamina have not been an invariable feature of human malignant tumors of nerve sheaths. The absence of basal lamina in a malignant sheath tumor may be evidence of dedifferentiation. (See Supplement to Fascicle 6.)

Stigmata and the diagnosis of neurofibromatosis. The clinical criteria for the diagnosis of neurofibromatosis have been evaluated (Riccardi). Café au lait spots, even in large numbers, are not in themselves diagnostic. Other ancillary features include Lisch nodules of the iris, pruritus associated with concentrations of neurofibromas, areolar neurofibromas in postpubertal females, hyperpigmentation over neurofibromas, and two levels of pigmentation in some café au lait spots.

Pseudogynecomastia has been observed in von Recklinghausen's disease. In some examples, the enlargement of the breasts is related to interlobular stromal hyperplasia. In the densely fibrous stroma, some of the fibroblasts are multinucleated (Lipper et al.; figs. 247, 248).

In one family with von Recklinghausen's disease, a peculiar, peritubular nodular sclerosis has been noted (Mandybur and Weiss) in the kidneys.

Megacolon may complicate neurofibromatosis (Bolande). The myenteric plexuses may show neurofibromatous or ganglioneuromatous hyperplasia (Bolande).

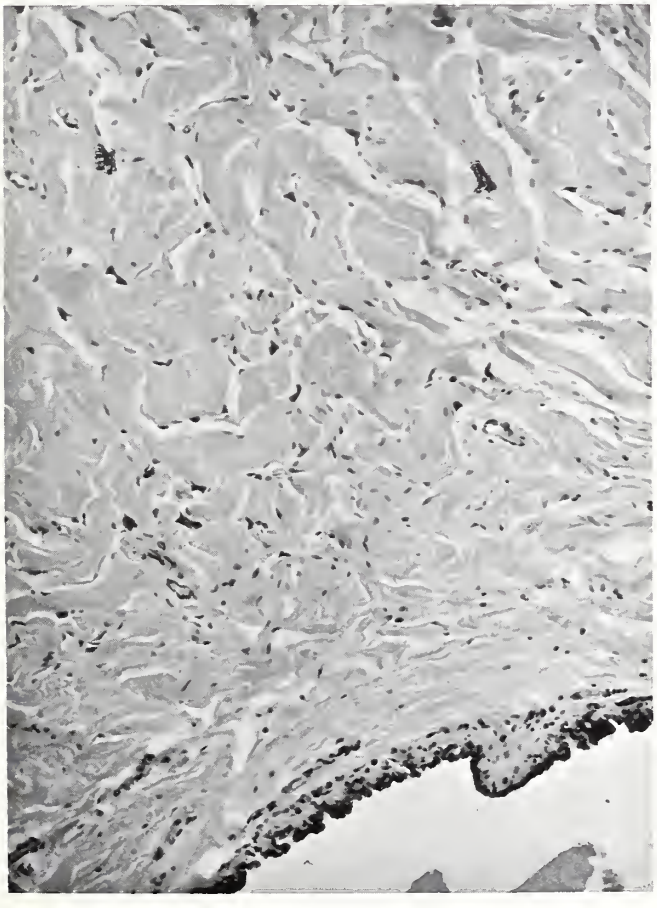

Figure 247
NEUROFIBROMATOSIS
The interlobular stroma is composed of coarsened collagen bundles and hyperplastic fibrocytes with plump irregular nuclei. The fibrocytes are stellate in outline. X97.

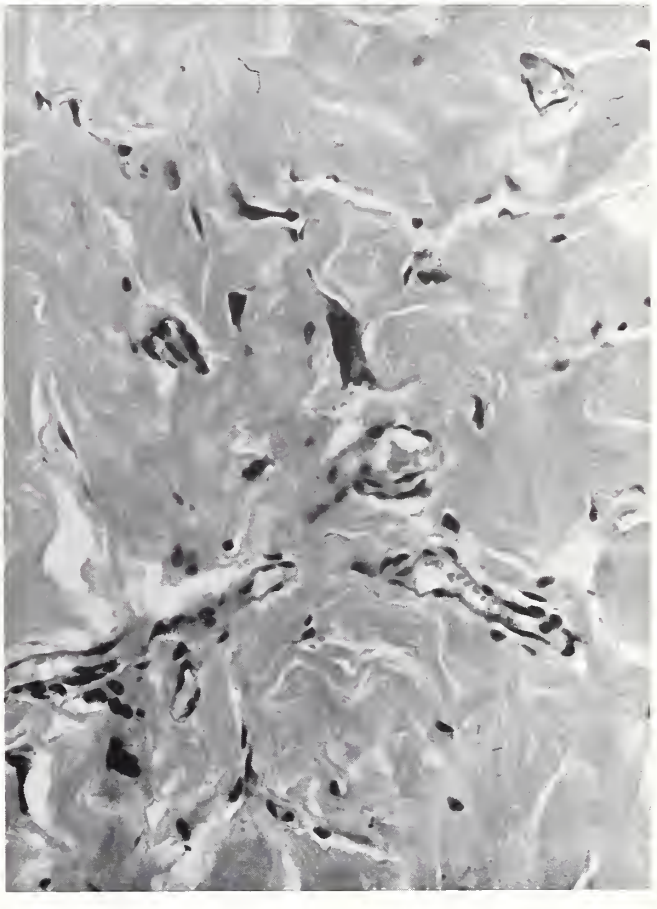

Figure 248
NEUROFIBROMATOSIS
A characteristic multinucleated fibrocyte is stellate in outline. These changes are manifested in some examples of pseudogynecomastia in von Recklinghausen's disease. X240.

References

Bolande, R. P. Neurofibromatosis — The Quintessential Neurocristopathy: Pathogenetic Concepts and Relationships, pp. 67-75. In: Advances in Neurology, Vol. 29, Neurofibromatosis. Riccardi, V. M. and Mulvihill, J. J. (Eds.). New York: Raven Press, 1981.

Cravioto, H., Weiss, J. F., Weiss, E. de C., Goebel, H. H., and Ransohoff, J. Biological characteristics of peripheral nerve tumors induced with ethylnitrosourea. Acta Neuropathol. 23:265-280, 1973.

Dible, J. H. Verocay bodies and pseudomeissnerian corpuscles. J. Pathol. Bacteriol. 85:425-433, 1963.

Eldridge, R. Central Neurofibromatosis with Bilateral Acoustic Neuroma, pp. 57-65. In: Advances in Neurology, Vol. 29, Neurofibromatosis. Riccardi, V. M. and Mulvihill, J. J. (Eds.). New York: Raven Press, 1981.

Foley, K. M., Woodruff, J. M., Ellis, F. T., and Posner, J. B. Radiation-induced malignant and atypical peripheral nerve sheath tumors. Ann. Neurol. 7:311-318, 1980.

Kanter, W. R., Eldridge, R., Fabricant, R., Allen, J. C., and Koerber, T. Central neurofibromatosis with bilateral acoustic neuroma: Genetic, clinical and biochemical distinctions from peripheral neurofibromatosis. Neurology 30:851-859, 1980.

Lipper, S., Willson, C. F., and Copeland, K. C. Pseudogynecomastia due to neurofibromatosis. Hum. Pathol. 12:755-759, 1981.

Mandybur, T. I. and Weiss, M. A. Sclerosing peritubular nodules: A hereditary renal abnormality in von Recklinghausen's disease. Hum. Pathol. 12:704-712, 1981.

Patchefsky, A. S., Atkinson, W. G., Hoch, W. S., Gordon, G., and Lipshitz, H. I. Interstitial pulmonary fibrosis and von Recklinghausen's disease. Chest 64:459-464, 1973.

Rezaian, S. M. The incidence of scoliosis due to neurofibromatosis. Acta Orthop. Scand. 47:534-539, 1976.

Riccardi, V. M. Pathophysiology of neurofibromatosis. IV. Dermatologic insights into heterogeneity and pathogenesis. J. Am. Acad. Derm. 3:157-166, 1980.

Smith, T. W. and Bhawan, J. Tactile-like structures in neurofibromas. Acta Neuropathol. 50:233-236, 1980.

Webb, W. R. and Goodman, P. C. Fibrosing alveolitis in patients with neurofibromatosis. Radiology 122:289-293, 1977.

INDEX

Anatomy
  axons, S-1
  endoneurium, S-1
  epineurium, S-2
  neurosustentacular system, S-2
  perineurium, S-1
  sheath cells, S-1
Anatomy, microscopic
  fibromas, storiform, perineurial, S-15, **S-15**, S-16
  melanomas, desmoplastic, S-41, **S-41**, S-42, **S-42**
  myxomas, perineurial, S-16, S-17, **S-17**
  neoplasms, perineurial, S-14, S-15
  neuritis, interdigital, S-4, **S-4**, S-5, **S-5**
  neurocarcinomas, peripheral, S-39, **S-39**
  neurofibromas, plexiform, S-22, **S-22**, S-23, **S-23**
  neurofibromas, symmetrical, **S-26**, S-27
  neurofibromatosis, **S-49**
  neuromas, S-6, S-7, **S-7**, **S-8**
  neuromas, pacinian, S-9, **S-9**, S-10
  neuromesenchymomas, malignant, S-29
  paraneurofibromas, **S-20**
  schwannomas, S-11—S-13, **S-11—S-13**
  schwannomas, composite, S-17, **S-18**
  schwannomas, granular cell, **S-14**, S-15
  schwannomas, malignant, epithelioid, S-31, **S-32**, S-33, **S-33**, **S-34**, **S-37**
  schwannomas, plexiform, S-12, **S-12**, S-13, **S-13**
  small cell tumor, malignant undifferentiated, S-39, **S-39**
Axons
  anatomy, S-1
  hyperplasia, S-6

Carcinogens
  nitrosoureas, induced peripheral nerve tumors, S-48
Classification
  nerve sheath tumors, malignant, S-28, S-29

Diagnosis, differential
  fibromas, storiform, perineurial, S-16
  neuromas, pacinian, S-10
  sarcomas, clear cell, S-47
Dysplasias, tumorous, S-6

Endoneurium
  anatomy, S-1
Epineurium
  anatomy, S-2

Fibromas, storiform, perineurial
  anatomy, microscopic, S-15, **S-15**, S-16
  diagnosis, differential, S-16
  nomenclature, S-15
Fibrosis, interstitial, pulmonary
  and neurofibromatosis, S-48

Genetics
  neuromas, S-6

Hyperplasia
  axons, S-6

Melanocytes, spindle, S-41, **S-41**, S-42, **S-42**
Melanomas, desmoplastic, S-41, **S-41**, S-42, **S-42**
Melanomas, neurotropic
  anatomy, microscopic, S-42, S-43, **S-42—S-45**, S-46
  embryology, S-41
Minimal deviation variant
  nomenclature, S-30
Morton's neuroma, see Neuritis, interdigital
Myxomas, perineurial
  anatomy, microscopic, S-16, S-17, **S-17**
  composite, S-17, **S-18**
  nomenclature, S-16

Neoplasms, perineurial
  anatomy, microscopic, S-14, S-15
  fibromas, storiform, perineurial, S-15, **S-15**, S-16
  myxomas, perineurial, S-16, S-17, **S-17**
Nerve sheath myxomas, see Myxomas, perineurial
Nerve sheath tumors, malignant
  classification, S-28, S-29
  nomenclature, S-28, S-29
Neuritis, interdigital
  anatomy, microscopic, S-3, S-4, **S-5**
  nomenclature, S-3
  ultrastructure, S-4, **S-4**, S-5
Neurocarcinomas, peripheral
  anatomy, microscopic, **S-38**, S-39, **S-39**
  glandular, **S-38**
Neuroepitheliomas of peripheral nerves
  anatomy, microscopic, **S-38**, **S-39**
  nomenclature, S-39
Neurofibromas
  with multifocal schwannomatosis, S-12
Neurofibromas, circumscribed
  nomenclature, S-22
Neurofibromas, diffuse, see Paraneurofibromas
Neurofibromas, plexiform
  anatomy, microscopic, S-22, **S-22**, S-23, **S-23**
  fibrous, S-23
  mucinous, S-23
Neurofibromas, plexiform, epithelioid
  nomenclature, S-25
Neurofibromas, symmetrical
  anatomy, microscopic, **S-26**, S-27
  nomenclature, S-25

Neurofibromatosis
anatomy, microscopic, **S-49**
and interstitial pulmonary fibrosis, S-48
and scoliosis, S-48
central variants, S-48
diagnosis, S-49
peripheral variants, S-48
stigmata, S-49

Neuromas
anatomy, microscopic, S-6, S-7, **S-7, S-8**
genetics, S-6
nomenclature, S-6
Neuromas, pacinian
anatomy, microscopic, S-9, **S-9,** S-10
diagnosis, differential, S-10
Neuromesenchyme
dysplasias, tumors, S-19—S-21
nomenclature, S-19
paraneurofibromas, **S-20**
Neuromesenchymomas, malignant
anatomy, microscopic, S-29
minimal deviation variant, S-30
nomenclature, S-29, S-30
prognosis, S-30
Neurosustentacular system
anatomy, S-2
Nitrosoureas
carcinogens, peripheral nerve tumor induction, S-48
Nomenclature
fibromas, storiform, perineurial, S-15
myxomas, perineurial, S-16
nerve sheath tumors, malignant, S-28, S-29
neuritis, interdigital, S-3
neurofibromas, plexiform, epithelioid, S-25
neurofibromas, symmetrical, S-25
neuromas, S-6
neuromesenchyme, S-19
neuromesenchymomas, malignant, S-29, S-30
sarcomas, clear cell, S-47
schwannomas, malignant, epithelioid, S-30, S-31
schwannomas, malignant, epithelioid, diffuse, S-35

Paraneurofibromas
anatomy, microscopic, **S-20,** S-24, **S-24**
aneurysmal, S-24, **S-25**
nomenclature, S-24
Perineurium
anatomy, S-1

Radiation
and malignant tumors of the nerve sheaths, S-48

Sarcomas, clear cell
diagnosis, differential, S-47
nomenclature, S-47
Schwannomas
anatomy, microscopic, S-11—S-13, **S-11**
nomenclature, S-11, S-28
Schwannomas, aneurysmal, S-13
Schwannomas, composite, S-17, **S-18**
Schwannomas, cystic, S-13
Schwannomas, epithelioid, S-13
Schwannomas, granular cell
anatomy, microscopic, **S-14,** S-15
Schwannomas, malignant epithelioid
anatomy, microscopic, S-31, **S-32,** S-33, **S-33, S-34,** S-37
nomenclature, S-28, S-30, S-31
Schwannomas, malignant, epithelioid, diffuse
anatomy, microscopic, S-35, **S-35—S-37**
minimal deviation variant, S-33, **S-33**
nomenclature, S-35
prognosis, S-35
Schwannomas, malignant, glandular, S-35, **S-38**
Schwannomas, plexiform, S-12, **S-12,** S-13, **S-13**
Scoliosis
and neurofibromatosis, S-48
Sheath cells
anatomy, S-1
Small cell tumors
malignant, undifferentiated, S-39, **S-39**

Tactoid bodies, S-48
Tumors, granular cell, S-15

Ultrastructure
endoneurium, S-1
neuritis, interdigital, S-4, **S-4,** S-5

PRINTED BY THE ARMED FORCES INSTITUTE OF PATHOLOGY

NIH Library, Building 10
National Institutes of Health
Bethesda, MD 20892

DATE DUE

GAYLORD PRINTED IN U.S.A.

LIBRARY
NIH
Amazing Research.
Amazing Help.

http://nihlibrary.nih.gov

10 Center Drive
Bethesda, MD 20892-1150
301-496-1080

NIH LIBRARY
4 0149 1139

NIH LIBRARY
3 1496 00195 0818

MAR 17 1987